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Lipid Metabolism Reprogramming of Tumor-Associated Macrophages in the Tumor Microenvironment

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ABSTRACT

Lipid metabolic reprogramming drives the pro-tumorigenic function of tumor-associated macrophages (TAMs) within the tumor microenvironment. Moving beyond the classical M1/M2 dichotomy, this review categorizes TAMs into functionally distinct lipid-associated subsets, each defined by unique metabolic dependencies. Specific lipid-derived metabolites act as instructive signaling molecules that directly orchestrate TAM polarization toward immunosuppression. Key pathways governing lipid uptake, *de novo* lipogenesis, fatty acid oxidation, and transcriptional control represent actionable therapeutic targets. Reprogramming TAM lipid metabolism offers a promising strategy to overcome immunotherapy resistance, enhance anti-tumor immunity, and improve cancer treatment outcomes. By integrating recent advances in single-cell technologies and preclinical models, this review provides a comprehensive framework for understanding lipid reprogramming as a central driver of TAM function and highlights new directions for precision metabolic immunotherapy.

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1. Introduction

The tumor microenvironment (TME) is a complex, self-organized, and dynamic ecosystem where cancer cells co-exist with a variety of heterogeneous stromal, immune, vascular endothelial cells, and pericytes, as well as adipocytes and nerve fibers, embedded in a remodeled extracellular matrix and shaped by soluble factors, metabolic stress, and aberrant physical properties [1, 2]. Among these, tumor-associated macrophages (TAMs) have emerged as central regulators of tumor progression, angiogenesis, metastasis, and immunosuppression [3, 4]. Derived from circulating monocytes or tissue-resident macrophages, TAMs are educated by the TME to acquire predominantly pro-tumorigenic phenotypes. Their remarkable functional plasticity enables them to transition between a spectrum of activation states, broadly categorized from pro-inflammatory, anti-tumorigenic (M1-like) to anti-inflammatory, pro-tumorigenic (M2-like) phenotypes [5-7]. However, the TME imposes a unique metabolic landscape, characterized by hypoxia, acidosis, nutrient competition, and an abundance of cellular debris that fundamentally rewires TAM biology.

Immunometabolism, a rapidly advancing discipline, has elucidated how immune cells metabolize nutrients to support their proliferation, differentiation, and effector functions [8, 9]. While the Warburg effect and glucose metabolism in cancer cells have been extensively studied, the metabolic wiring of immune cells within the TME, particularly TAMs, has only recently come into sharp focus [10]. It is now recognized that metabolic reprogramming is not merely a passive adaptive response to environmental stress but an active driver of TAM functional polarization. Among the various metabolic pathways, lipid metabolism has been identified as a central orchestrator of TAM biology, serving as a critical link be-

tween the TME's unique metabolite composition and the transcriptional programs that define TAM function [11, 12].

Lipids are far more than passive fuel sources or inert membrane components [13, 14]. They function as versatile signaling molecules, precursors for bioactive mediators, and key modulators of cellular processes such as membrane fluidity, organelle identity, and protein modification [13]. In immune cells, lipid metabolism directly influences activation, differentiation, and effector functions. Within the TME, aberrant tumor cell metabolism is characterized by upregulated fatty acid synthesis, enhanced lipid efflux, and increased rates of cell death.

This review aims to systematically summarize and discuss the role of lipids in the metabolic reprogramming of TAMs within the TME and their consequent regulation of biological functions. We will move beyond the classical M1/M2 dichotomy and classify TAMs into functionally validated subsets based on recent single-cell transcriptomic and metabolomic studies. By integrating recent advances in immunometabolism and tumor immunology, we aim to provide a comprehensive framework for understanding how lipid reprogramming governs TAM function and how this knowledge can be translated into effective cancer therapies.

Metabolism-related signaling pathway of TAM in TME

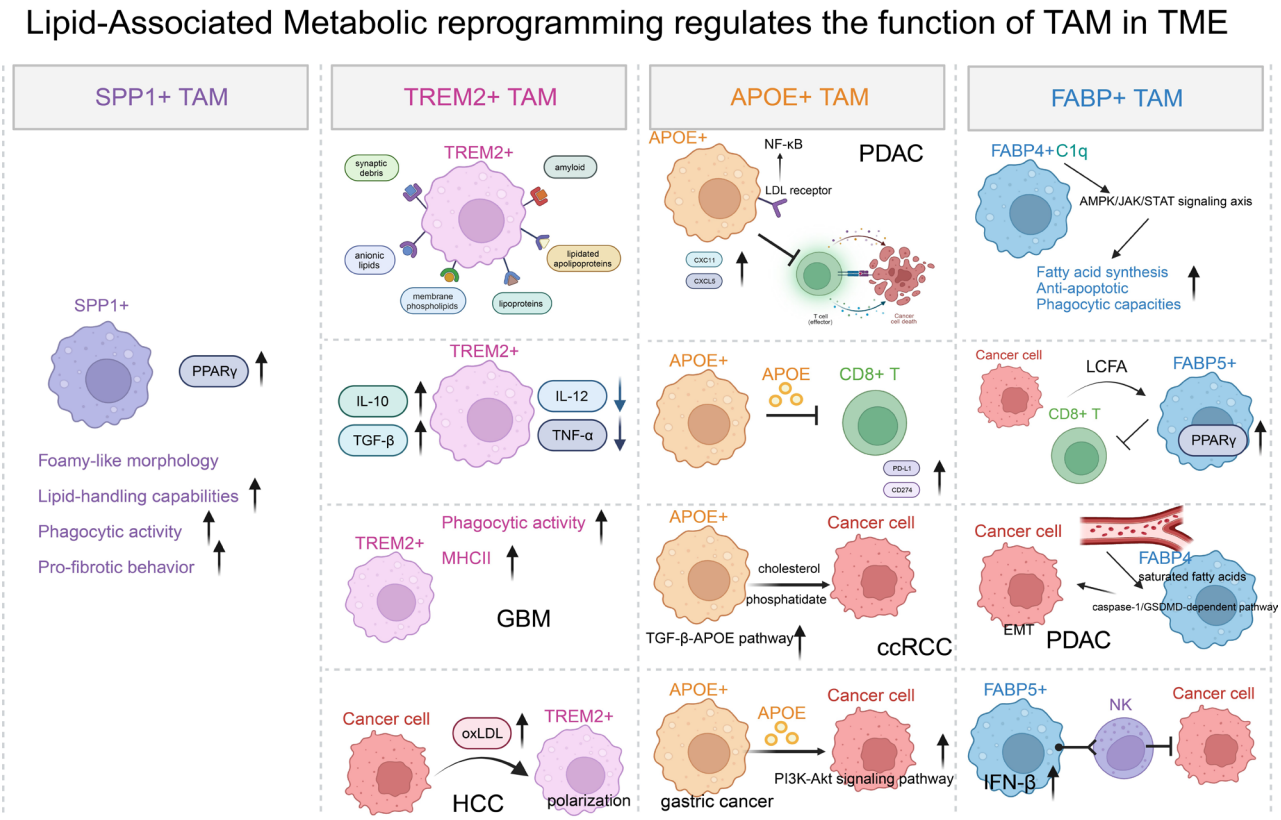
TAMs are extensively reprogrammed in their metabolic wiring upon entering the tumor microenvironment [15]. They adapt to the unique metabolite landscape of the TME, characterized by hypoxia, acidosis, nutrient competition, and an abundance of lipid-rich debris [16]. This adaptive process, termed metabolic reprogramming, is not merely a passive response but an active driver of TAM functional polarization and pro-tumorigenic behavior.

Glucose is the main energy source for macrophages, with its metabolism occurring primarily through glycolysis, the tricarboxylic acid (TCA) cycle, and the pentose phosphate pathway (PPP) for rapid ATP generation [17]. Following exposure to pro-inflammatory stimuli such as LPS and IFN-γ, classically activated M1-like macrophages undergo a substantial metabolic shift characterized by markedly enhanced glycolysis [18, 19]. Conversely, alternatively activated M2-like macrophages, induced by cytokines including IL-4 and IL-13, depend on an unimpaired TCA cycle and sustained oxidative phosphorylation (OXPHOS) as their predominant pathway for energy production [20, 21]. However, TAMs in the tumor microenvironment do not strictly follow either of these classical patterns. Across diverse cancer types, TAMs exhibit concurrent activation of the TCA cycle and fatty acid oxidation (FAO), a metabolic configuration that facilitates the utilization of alternative carbon substrates, most notably glutamine [22-25]. TAMs upregulate glutamine synthetase (GS) activity, a metabolic adjustment that both supports de novo nucleotide synthesis and drives immune evasion alongside angiogenesis [26]. Much like alternatively M2-like macrophages, pro-tumorigenic TAMs exhibit enhanced fatty acid uptake and glutamine utilization, coupled with elevated OXPHOS activity. These metabolic features underpin their tumor-promoting phenotypes and ultimately facilitate tumor progression [27, 28].

Beyond glucose and lipid metabolism, amino acid handling also distinguishes TAMs from classically activated macrophages. Arginine metabolism plays a critical role in shaping macrophage responses. The conversion of arginine to nitric oxide (NO) is essential for mounting effective antimicrobial and pro-inflammatory reactions. In contrast, arginase 1 (ARG1) mediates a metabolic shift from NO production toward polyamine synthesis, thereby suppressing inflammation and facilitating the restoration of tissue homeostasis [29]. Collagen internalized by TAMs serves as an abundant reservoir of arginine, which is subsequently metabolized via ARG1 and iNOS pathways [30, 31].

The lipid-rich TME arises from aberrant tumor cell metabolism, which further shapes TAM functional polarization. In contrast to normal tissue cells, tumor cells frequently exhibit disrupted lipid metabolism, characterized by upregulated fatty acid synthesis and enhanced lipid efflux, which collectively contribute to lipid-enriched TME [32-34]. Consequently, in this environment where necrotic cellular debris, shed lipoproteins, and exogenous fatty acids accumulate, TAMs enhance expression of the scavenger receptor CD36 [35-37]. This receptor facilitates lipid internalization, leading to marked intracellular lipid deposition, and stored lipids subsequently serve as fuel for FAO, which produces ATP and reinforces the immunosuppressive, pro-tumorigenic phenotype. Furthermore, elevated FAO not only sustains cellular energy balance but also drives the production of anti-inflammatory cytokines, including IL-10 and TGF-β [38, 39].

Figure 1. Lipid-Associated Metabolic reprogramming regulates the function of TAM in TME.



Collectively, these studies reveal that TAMs operate a hybrid metabolic program that blends elements of glycolysis, FAO, TCA cycle activity, and amino acid catabolism. TAMs adopt a unique metabolic configuration that defies the conventional M1/M2 dichotomy, blending glycolysis, FAO, TCA cycle activity, and amino acid catabolism into a pro-tumorigenic metabolic program. Lipid metabolism, which is shaped by a network of signalling pathways that translate environmental cues into functional outputs. Understanding these integrated metabolic–signalling circuits offers opportunities for therapeutic intervention aimed at rewiring TAM metabolism to restore antitumour immunity.

2. Lipid-Associated Metabolic reprogramming regulates the function of TAM in TME.

Playing a vital role in cellular homeostasis, lipid metabolism involves the synthesis and degradation of lipids. Emerging studies have underscored that lipids serve as crucial regulators of cellular function, especially in TAMs, where lipid metabolism influences functions, their phenotypes, metabolic pathways, and cytokine production. TAMs are pivotal regulators within the TME, exhibiting a spectrum of functional states often simplified as anti-tumor (M1-like) and pro-tumor (M2-like) phenotypes [40]. Advances in single-cell transcriptomics and metabolomics have unveiled a richer landscape, identifying distinct TAM subpopulations with unique metabolic dependencies [41]. Therefore, in this section, we will move beyond the classical M1/M2 dichotomy and classify TAMs into more detailed, functionally validated subsets to discuss the profound impact of lipid metabolic reprogramming on their biology (**Figure 1**).

2.1 SPP1⁺ TAM

SPP1 (Secreted Phosphoprotein 1), commonly known as osteopontin (OPN), plays a pivotal and multi-faceted role in the function and polarization of TAMs [42]. SPP1⁺ TAMs have been identified as key orchestrators of the immunosuppressive TME, particularly in highly aggressive tumors such as glioblastoma [43], hepatocellular carcinoma [44], colorectal cancer [45], and prostate cancer [46]. Moreover, SPP1⁺ TAMs can simultaneously interact with various cell types in the immune microenvironment to regulate cancer immune responses. For example,

FAP$^+$ fibroblasts and SPP1$^+$ macrophages co-localize in CRC, driven by chemerin/TGF-β/IL-1, forming immune-excluded stroma that limits T cells and the anti-PD-L1 response [47]. Ruben Bill et al. demonstrated that macrophage polarity defined by CXCL9 and SPP1 (CS) expression, CS polarity orchestrates a highly coordinated, spatially organized network of pro- or antitumor variables across all tumor-associated cell types, a finding extended to multiple cancers [48]. In prostate cancer, SPP1^{hi}-TAMs become enriched with the progression of prostate cancer to mCRPC performs as key mediators of resistance to immune checkpoint inhibitors in advanced metastatic castration-resistant prostate cancer (mCRPC) through adenosine signalling [46].

The lipid metabolic program of SPP1$^+$ TAMs is intimately linked to their pro-tumorigenic functions. SPP1$^+$ TAMs in liver cancer are characterized by a terminally differentiated state and reliance on PPARγ; some studies indicated that SPP1$^+$ TAMs adopt a foamy-like morphology and show enhanced lipid metabolism as well as elevated phagocytic activity [49]. In lung cancer, A population of TREM2$^+$ TAMs co-expressing the SPP1$^+$ gene signature was identified in the pulmonary microenvironment, where these cells display lipid-handling capabilities and pro-fibrotic behavior in response to local cues [50]. A distinct SPP1$^+$ macrophage subpopulation with lipid associate signature has been identified in pancreatic ductal adenocarcinoma, which points to functions in lipid metabolism and phagocytosis, potentially remodeling the metabolic landscape of the tumor microenvironment [51].

Collectively, SPP1$^+$ TAMs act as pivotal orchestrators within the immunosuppressive tumor microenvironment across various aggressive cancers. SPP1$^+$ macrophages closely intertwine metabolic reprogramming with pro-tumorigenic and pro-fibrotic functions.

2.2 TREM2$^+$ TAM

TREM2 (Triggering Receptor Expressed on Myeloid cells 2) has recently emerged as a defining marker of a unique and highly immunosuppressive TAM subpopulation [52-54], and its abundance often correlates with poor prognosis and resistance to immune checkpoint blockade (ICB) therapy. TREM2 initiates phagocytosis by recognizing and binding a diverse array of target ligands, including anionic lipids, membrane phospholipids, lipoproteins, lipidated apolipoproteins, synaptic debris, and amyloid-β [55-57]. The biology of TREM2$^+$ TAMs is intrinsically linked to the sensing and metabolism of lipids, particularly cholesterol and sphingolipids. For example, in prostate cancer, a specific AR$^+$TREM2$^+$ TAM subset enriched in lipid metabolism drives pathogenic immunosuppression, and co-targeting TREM2 with androgen receptor blockade significantly blunts tumor progression [58].

One of the most striking features of TREM2$^+$ TAMs is to detect and counteract the loss of tissue-level lipid homeostasis [59]. The functional outcome of lipid reprogramming is the establishment of a profoundly anti-inflammatory and pro-tumorigenic state. TREM2$^+$ TAMs produce high levels of interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), while suppressing the production of pro-inflammatory cytokines like IL-12 and TNF-α [60, 61]. Similarly, some studies indicated that TREM2 is highly expressed in brain tumor myeloid cells, including microglia and macrophages, they deficiency accelerates glioma progression by impairing the TAM ability to phagocytose tumor cells and reducing MHCII expression. This ultimately decreases protective CD4$^+$ T-cell infiltration within the tumor hemispheres, revealing TREM2$^+$ TAMs' crucial anti-tumor role [62].

Certain tumor-derived lipid metabolites can similarly modulate TREM2$^+$ TAM functionality, consequently suppressing anti-tumor immunity. For example, in hepatocellular carcinoma (HCC), elevated cancer-cell SQLE generates oxLDL, driving TREM2$^+$ TAM polarization through the TREM2-SYK-CEBP-alpha axis [63]. Reciprocally, these TREM2$^+$ TAMs can support HCC by recycling fatty acids via efferocytosis, driving epigenetic adaptations that cause metabolic resistance to ICB therapy [64]. Moreover, TREM2 deficiency causes the downregulation of the cholesterol transporter ABCA1. This triggers intracellular cholesterol accumulation within TAMs, forcing them to shift toward a pro-inflammatory phenotype. These reprogrammed, pro-inflammatory macrophages secrete higher levels of the chemokine CX3CL1, which actively recruits CD4$^+$ T and NK cells to the tumor site to mount a robust anti-tumor response [65]

In summary, TREM2 acts as a master lipid-sensing receptor that dictates TAM polarization through metabolic reprogramming. By recognizing extracellular lipids, TREM2 balances tissue lipid homeostasis, typically driving TAMs toward an immunosuppressive, pro-tumor state that secretes anti-inflammatory cytokines.

2.3 APOE⁺ TAM

APOE (Apolipoprotein E) is a multifunctional protein with central roles in lipid transport and metabolism [66-69]. The source of these lipids includes tumor-derived fatty acids, oxLDL, and apoptotic cell membranes. A distinct subpopulation of TAMs characterized by high APOE expression has been identified and is often associated with immune suppression and tumor progression, though context-dependent anti-tumor roles have also been reported [70, 71]. The functional duality of APOE⁺ TAMs is resolved by understanding the nuances of their lipid metabolic state. For example, Samantha B Kemp et al. reveal that APOE⁺ TAMs in peripheral blood monocytes of PDAC patients serve as a survival-stratifying biomarker. APOE deficiency reduces tumor growth and increases CD8⁺ T cells, as APOE mechanistically drives immunosuppression by inducing CXCL1 and CXCL5 expression via LDL receptor/NF-κB signaling [72]. In early-onset prostate cancer, single-cell and spatial transcriptomics have revealed that APOE⁺ TAMs specifically infiltrate tumor cells with activated androgen responses, thereby facilitating tumor progression and shaping an immunosuppressive microenvironment [73].

The secreted APOE assembles with phospholipids and cholesterol to form lipoprotein particles [74]. APOE particles that are small and lipid-poor are efficient at accepting cholesterol from the ABCA1 transporter, a process that reduces cellular lipid stress and promotes an anti-inflammatory, M2-like state [75]. APOE particles that are large and lipid-rich can activate several signaling pathways. They can bind to members of the LDL receptor family, such as LRP1 (LDL receptor-related protein 1) [76, 77]. LRP1 signaling in macrophages can suppress inflammatory responses and promote cell survival. Critically, APOE-LRP1 signaling can induce the expression of immune checkpoint molecules like PD-L1 and CD274, directly contributing to the immunosuppressive capacity of these TAMs by inhibiting T cell function [78]. Similarly, recently study indicated that TAMs undergo immunometabolism reprogramming via a TGF-β-APOE-dependent pathway to become lipid-laden. These macrophages directly transfer cholesterol and phosphatidates to VHL-deficient ccRCC cells via tunneling nanotubes (TNTs) [79]. Eleonora Ghisoni et al report that recurrent ovarian cancers mimic the immune landscapes of original tumors. In wild-type BRCA tumors, the loss of immune-stimulating niches leads to an immunosuppressive environment driven by specific TREM2⁺APOE⁺ macrophage networks [80]. Moreover, recently study shows that APOE⁺ TAMs are enriched in gastric cancer and promote cell migration. M2 macrophage-derived exosomes act as a vehicle to deliver functional Apolipoprotein E directly into recipient gastric cancer cells. This transferred Apolipoprotein E triggers the activation of the PI3K-Akt signaling pathway in cancer cells [81].

In summary, APOE acts as a critical "metabolic-immune checkpoint" orchestrating the lipid reprogramming of TAMs. Mechanistically, APOE drives TAMs to directly provision tumor cells with lipids, either via exosomes in cancer or tunneling nanotubes. APOE-mediated direct transfer represents a promising therapeutic frontier to dismantle TME immune tolerance and synergize with conventional immunotherapies.

2.4 FABP⁺ TAM

Fatty acid-binding proteins (FABPs), particularly FABP4 and FABP5, are intracellular lipid chaperones that regulate fatty acid transport, storage, and signaling [82-84]. Elevated FABP expression in TAMs has been identified across diverse malignancies [85-88]. Unlike other markers that primarily sense extracellular lipids, FABPs directly orchestrate cytosolic lipid handling, thereby linking metabolic flux to TAM functional polarization and constituting a critical node in TAM metabolic reprogramming. For example, single-cell analysis of osteosarcoma reveals that lung metastases are characterized by a high proinflammatory FABP4⁺ TAM infiltration, alongside significantly lower osteoclast levels in chondroblastic, recurrent, and metastatic lesions compared to primary tumors. Within this specialized immunosuppressive metastatic niche, blocking the TIGIT checkpoint effectively restores CD3⁺ T-cell cytotoxicity, highlighting a promising therapeutic target to overcome immunosuppression [89]. Research demonstrates that FABP4 and C1q work synergistically to regulate the expression of proinflammatory cytokines. Through crosstalk with the AMPK/JAK/STAT signaling axis, they promote fatty acid synthesis while enhancing both the anti-apoptotic and phagocytic capacities of macrophages, revealing FABP4 as a central hub integrating metabolism and immune function [90]. In pancreatic neuroendocrine neoplasm, hypoxic tumor-derived exosomal miR-4488 drives macrophage M2-like polarization by suppressing RTN3. Mechanistically, this suppression downregulates FABP5, enhancing fatty acid oxidation and activating the PI3K/

AKT/mTOR pathway. These polarized macrophages secrete MMP2, establishing a positive feedback loop that fosters a premetastatic niche and promotes liver metastasis [91]. Similarly, Single-cell sequencing identified immunosuppressive, lipid-loaded FABP5$^+$ TAMs in hepatocellular carcinoma. Mechanistically, tumor-derived long-chain unsaturated fatty acids activate PPAR-γ via FABP5 to drive this immunosuppression. Consequently, FABP5 deficiency in macrophages reduces immunosuppressive molecules, enhances T-cell antitumor immunity, slows tumor growth, and boosts immunotherapy efficacy [92].

In obese conditions, elevated serum FABP4 drives pancreatic cancer progression by promoting macrophage-related inflammation. Mechanistically, FABP4 transfers saturated fatty acids to induce macrophage pyroptosis via a caspase-1/GSDMD-dependent pathway. This activates the NLRP3/IL-1β axis, triggering epithelial-mesenchymal transition (EMT) signals that accelerate cancer cell migration, invasion, and metastasis [93]. Moreover, a study demonstrates that unsaturated fatty acids (FAs), such as linoleic acids (LA), have a higher propensity to form lipid droplets in murine macrophages compared to saturated FAs. This preference arises because unsaturated fatty acids specifically activate the FABP4/CEBP-α pathway, which subsequently drives triglyceride synthesis and lipid droplet accumulation, indicating that different fatty acid species selectively reprogram TAM lipid metabolism [94].

However, FABP family members are not uniformly pro-tumorigenic; under certain contexts, specific FABPs exhibit antitumor activity. For example, Epidermal Fatty Acid-Binding Protein (E-FABP, FABP5) promotes antitumor activity by triggering lipid droplet formation in specific TAMs. This upregulation drives the production of Interferon-beta (IFN-β) within the tumor stroma, which subsequently recruits natural killer (NK) cells to actively restrict and suppress tumor growth [95]. This finding reveals a bridging role for FABP5 between lipid droplet formation and innate immune activation, contrasting sharply with the pro-tumor function of FABP5 in liver cancer and suggesting that FABP5's role is highly dependent on tumor type and metabolic microenvironment. Moreover, while both cocoa butter and fish oil high-fat diets cause similar obesity in mice, fish oil uncouples obesity from mammary tumor growth. Its omega-3 fatty acids induce reactive oxygen species (ROS) to kill protumor TAMs via an A-FABP-dependent (A-FABP, FABP4) pathway, demonstrating that not all obesity-inducing diets are tumorigenic [96]. A study identifies A-FABP as a key marker in a specific subset of TAMs that drives breast cancer progression. High A-FABP expression correlates with lower survival, while its deficiency reduces tumor growth and metastasis by suppressing protumor IL-6/STAT3 signaling via the NF-κB/miR-29b pathway [97].

In summary, FABP4 and FABP5 act as metabolic switches in TAMs, driving either immunosuppressive M2 polarization or antitumor immunity depending on tumor context, fatty acid composition, and upstream signals. Future strategies should combine FABP modulation with immune checkpoint blockade.

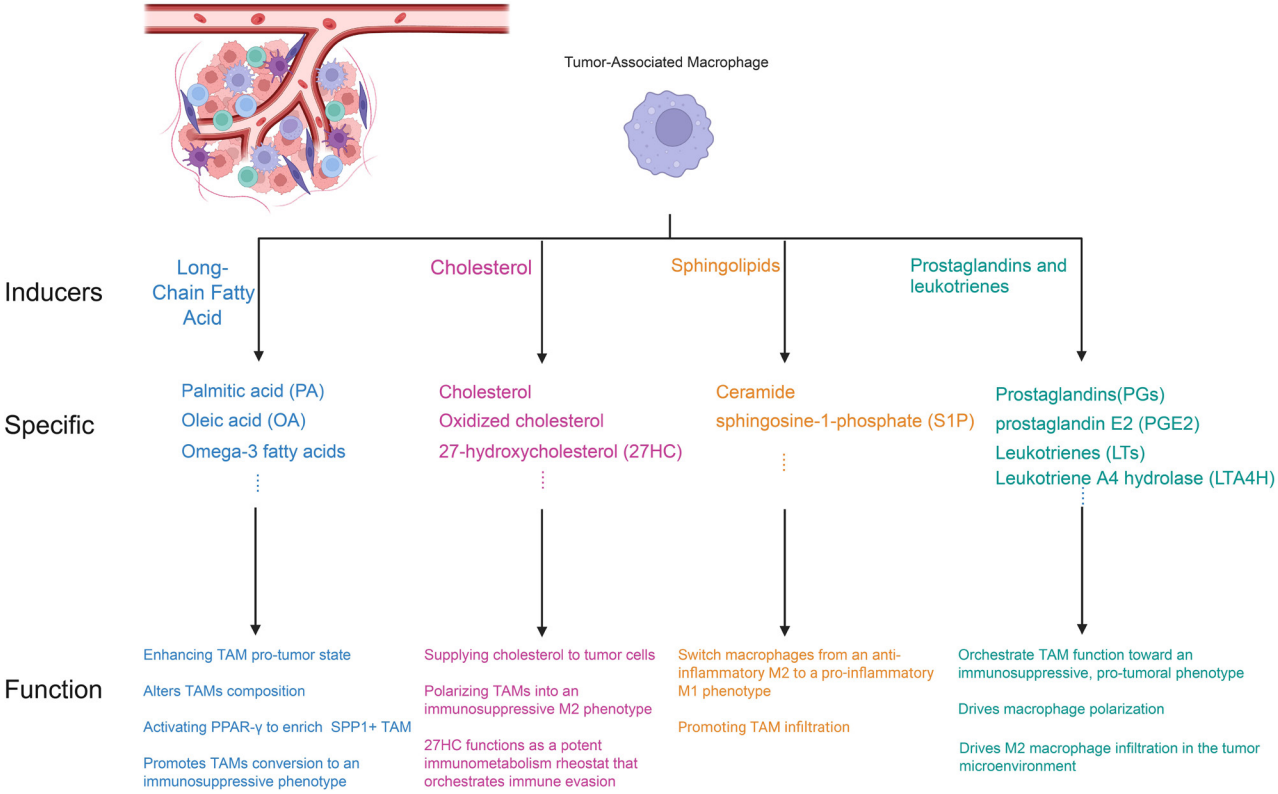
2.5 Other Markers

Beyond the major subsets discussed above, emerging single-cell and spatial transcriptomic studies have identified additional lipid-associated markers that define functionally distinct TAM subpopulations. These include GPNMB (Glycoprotein Non-metastatic Melanoma Protein B), CD36, and PLIN2 (adipose differentiation-related protein).

GPNMB$^+$ TAMs have been characterized in colorectal liver metastasis as a negative prognostic indicator and a potential player in the protumor function of TAMs and profound immunosuppressive activity. Nina Cortese et al demonstrate that differentiated GPNMB$^+$ TAMs drive matrix degradation, angiogenesis, and lipid metabolism near the tumor margin, correlating with shorter survival [98]. CD36, a scavenger receptor mediating fatty acid uptake, defines a pro-tumorigenic TAM subpopulation across multiple cancers [99, 100]. Pan Su et al report that TAMs accumulate lipids in the tumor microenvironment via the scavenger receptor CD36 and utilize fatty acid oxidation for energy production. This metabolic shift triggers a JAK1/STAT6 signaling pathway that drives protumor TAM differentiation and activation, suggesting that targeting FAO could serve as a cancer therapy [35]. Another lipid-droplet-associated protein, PLIN2, has recently emerged as a key functional marker in cancer. Single-cell analysis of ovarian cancer identified lipid-loaded, PLIN2$^+$ TAMs that drive cancer progression. PLIN2 links lipid metabolism to hypoxia by boosting HIF1-alpha and SPP1 signaling, enhancing tumor cell migration, invasion, and vascular permeability. Targeting PLIN2 with liposomes successfully suppresses ascites production and trans-coelomic metastasis [101].

Collectively, these additional markers underscore the heterogeneity of lipid-associated TAM repro-

Figure 2. Specific lipid-associated metabolites orchestrating the fate of TAM.



gramming. The continued discovery of these markers through high-dimensional technologies will enable precise targeting of metabolic vulnerabilities across the spectrum of TAM subpopulations.

3. Specific Lipid-Associated Metabolite Orchestrating the Fate of TAM.

Beyond the classification of TAM subsets, specific lipid-derived metabolites act as powerful signaling molecules that directly orchestrate TAM polarization and function within the TME [102, 103]. These metabolites are not merely byproducts; they are instructive cues that dictate cellular fate (**Figure 2**).

3.1 Long-Chain Fatty Acid

Palmitic acid (PA, C16:0) is the most abundant circulating saturated fatty acid and serves as both an energy substrate and a potent signaling molecule within the TME [104-106]. For example, Gang Wang et al demonstrate that tumor-derived extracellular vesicles and particles (EVPs) use palmitic acid to trigger a damaging chain reaction in the liver [107]. Emerging evidence positions PA as a key instructive metabolite that directly shapes TAM function, differentiation, and crosstalk with tumor cells through multiple interconnected mechanisms [108-110]. In prostate cancer, palmitic acid binds to the chemosensor OR51E2 on TAMs, enhancing this protumor state. Deleting these receptors *in vivo* triggers cancer regression and boosts antitumor $CD8^+$ T cell infiltration [111]. Palmitic acid can also determine the fate of TAMs in the tumor microenvironment through indirect effects. A study illustrates that tumor-derived palmitic acid activates a TLR4/Syk/NF-κB signaling cascade in fibroblasts and secretes IL-6, driving glutamine synthesis, ultimately altering TAM composition to promote an immunosuppressive tumor microenvironment [112].

Beyond palmitic acid, other long-chain fatty acids (LCFAs, typically with 14–20 carbons) have emerged as critical lipid-derived metabolites that actively instruct TAM behavior within the TME [92]. This phenomenon has been reported extensively in liver cancer. For instance, SLC27A2 downregulation reduces LCFAs intake in hepatocellular carcinoma, preventing lipid peroxidation toxicity under hypoxia. These deficient cells become sensitive to metabolic inhibitors. Unabsorbed LCFAs are instead redistributed to TAM, activating PPAR-γ to enrich immunosuppressive $SPP1^+$ TAM, which simultaneously creates vulnerability to anti-PD-1 therapy [113]. Interestingly, Clonorchis sinensis infection promotes intrahepatic cholangiocarcinoma progression by enriching fatty

acid synthase (FASN) and free fatty acids. This metabolic alteration drives an immunosuppressive microenvironment characterized by TAM infiltration and impaired T-cell function [114]. Similarly, HCC-derived oleic acid (OA) promotes TAMs conversion to an immunosuppressive phenotype [115-117]. In addition to saturated and monounsaturated long-chain fatty acids, polyunsaturated fatty acids (PUFAs), including omega-6 fatty acids and omega-3 fatty acids, actively shape TAM fate [118-121]. Xiao Lei Chen et al demonstrate that Focal adhesion kinase (FAK) inhibition or deficiency causes tumor cells to release exosomes enriched in omega-3 fatty acids. These tumor-derived lipids, alongside eicosapentaenoic acid, stimulate TAM to produce CXCL13 and undergo antitumor reprogramming, uncovering a lipid-macrophage signaling axis that could enhance immunotherapy [122]. Moreover, PUFAs in TAMs initiate ferroptosis, a form of iron-dependent regulated cell death marked by lipid peroxidation [123-125]. Collectively, these findings establish long-chain fatty acids as instructive signals that rewire TAM polarization, metabolic crosstalk, and immunotherapy response in the tumor microenvironment.

3.2 Cholesterol

Cholesterol and its derivatives have emerged as potent signaling entities that directly dictate TAM fate within the tumor microenvironment [126, 127]. A study reports that TAMs drive CRPC progression and therapeutic resistance by supplying cholesterol to tumor cells. This fuels intratumoral androgen biosynthesis and sustains nuclear androgen receptor signaling during deprivation therapy [128]. Single-cell and spatial transcriptomics of non-small cell lung cancer revealed that TAMs undergo transcriptional reprogramming, shifting toward cholesterol export and a fetal-like signature that promotes iron efflux [129]. In pancreatic cancer, lactate-driven histone lactylation transcriptionally activates ACAT2 in pancreatic cancer, stabilizing MTCH2 to disrupt oxidative phosphorylation and fuel a pro-lactate feedback loop. This loop promotes small extracellular vesicle-mediated cholesterol delivery, polarizing TAMs into an immunosuppressive M2 phenotype [130]. Similarly, oxidized cholesterols (oxysterols) are accumulated in the TME, generated by reactive oxygen species (ROS) produced by both tumor and immune cells [103, 131, 132].

27-hydroxycholesterol (27HC) is a primary oxidative metabolite of cholesterol, generated via the enzymatic activity of CYP27A1 (sterol 27-hydroxylase). Within the tumor microenvironment, 27HC functions as a potent immunometabolism rheostat that orchestrates immune evasion. Erik R Nelson et al. demonstrate that Hypercholesterolemia promotes ER-positive breast cancer through 27HC, driving ER-dependent growth and LXR-dependent metastasis. In humans, high CYP27A1 expression in tumor cells and macrophages correlates with elevated tumor grade, highlighting 27HC inhibition as a viable therapeutic strategy [133].

3.3 Sphingolipids

Ceramides are a family of waxy lipid molecules composed of a sphingoid base linked to a fatty acid via an amide bond [134], and dysregulation of ceramide metabolism is linked to cancer progression [135-137]. Regarding TAM, a study shows that Ceramide and palmitic acid switch macrophages from an anti-inflammatory M2 to a pro-inflammatory M1 phenotype. This shift inhibits M2-induced epithelial-mesenchymal transition (EMT) and migration in colorectal cancer cells by downregulating SNAI1, vimentin, IL-10, STAT3, and NF-κB, while upregulating E-cadherin to suppress tumor progression [108]. In addition, ginseng-derived nanoparticles (GDNPs) utilize their ceramide lipids and proteins to trigger TLR4 and MyD88 signaling. This pathway shifts tumor-supportive M2 macrophages to an anti-tumor M1 phenotype, generating reactive oxygen species that induce melanoma cell apoptosis and successfully suppress tumor growth in mice [138]. Thus, ceramides generally instruct TAMs to adopt an M1-like, anti-tumor fate.

Beyond Ceramides, sphingosine-1-phosphate (S1P) is another central metabolite in the sphingolipid network, which generally promotes an immunosuppressive tumor microenvironment [139]. S1P is generated from ceramide via the enzymatic activity of sphingosine kinases (SphK1/2), and its levels are frequently elevated in various cancers [140]. Focusing on TAMs, Yizhi Zhan et al recently illustrate that SPHK1-produced S1P triggers NLRP3 inflammasome and IL-1β release via NF-κB/HIF-1α signaling, promoting TAM infiltration and $CD8^+$ T cell exhaustion. Blocking SPHK1 combined with anti-PD-1 therapy reverses this immunosuppression, stalling metastasis and extending survival [141]. Interestingly, studies showed that whole beta-glucan particles (WGP) can control cancer metastasis by inducing trained immunity in pre-metastatic niche myeloid cells. This trained

phenotype is driven by a sphingosine-1-phosphate metabolic and mitochondrial fission pathway, which also activates human monocytes [142]. Collectively, S1P directs TAMs toward a pro-tumoral, immunosuppressive fate that facilitates immune evasion and metastatic progression.

3.4 Prostaglandins and leukotrienes

Prostaglandins (PGs) are best recognized for their roles as mediators of inflammation and hemostasis, which explains why aspirin is widely used to manage pain and inflammation as well as to serve as an antithrombotic agent [143]. Chemically, prostaglandins are oxygenated derivatives of arachidonic acid, a fatty acid that is not found freely within cells under normal conditions [144, 145]. Nowadays, prostaglandins have been recognized as one of the hallmark metabolites influencing immune responses within the tumor immune microenvironment [146]. Regarding their impact on TAMs, Nicoletta Caronni et al discovered that an inflammatory loop between pancreatic ductal adenocarcinoma (PDAC) cells and IL-1beta$^+$ TAMs drives cancer progression. Elicited by prostaglandin E2 (PGE2) and TNF synergy, these proximal macrophages induce pathogenic reprogramming in tumor cells early in tumorigenesis. Blocking the PGE2-IL-1beta$^+$ axis reprograms immune dynamics and controls PDAC growth *in vivo* [51]. Additionally, a subsequent study further shows that PGE-2 induces immunosuppression in the tumor microenvironment by impairing immune cell bioenergetics and ribosome biogenesis via EP2/EP4 receptors. Mechanistically, PGE-2 blocks IL-2-STAT5 signaling in CD8$^+$ T cells and downregulates c-Myc and oxidative phosphorylation in both T cells and M1-like macrophages, thereby hampering adaptive and innate antitumor immunity [147]. Interestingly, in microsatellite-stable (MSS) colorectal cancer, TAMs express high levels of COX1/2 and produce PGE_2, driving terminal CD8$^+$ T-cell exhaustion characterized by PD-1$^+$ TIGIT$^+$ co-expression. Inhibiting COX2, PGE_2 receptors, or M2-like TAMs blocks TIGIT upregulation and restores T-cell cytotoxicity, offering a strategy to overcome immunotherapy resistance in MSS tumors [148]. Similarly, in bladder cancer, memory-like CCL5^{hi} CD4$^+$ T cells promote antitumor immunity by driving M1-like macrophage polarization via CCL5/CCR1 signaling, correlating with positive immunotherapy responses. However, tumor-derived PEG2 suppresses the differentiation of these immunostimulatory T cells from CCR6^{hi} CD4$^+$ precursors, inducing resistance to immune checkpoint inhibition [149]. Collectively, prostaglandins, most notably PGE_2, act as central lipid mediators that orchestrate TAM function toward an immunosuppressive, pro-tumoral phenotype.

Both leukotrienes and prostaglandins belong to the eicosanoid family. They are active lipid mediators metabolically generated from arachidonic acid via the 5-lipoxygenase (5-LOX) pathway [150]. Leukotrienes (LTs) are also widely studied in the tumor immune microenvironment, where they play important roles in TAMs [151-153]. Specifically, regarding recent findings, an inflammatory mediator, Leukotriene A4 hydrolase (LTA4H), has become a focus of research for its contributions to the development of various cancers. LTA4H protects against hepatocellular carcinoma progression but is downregulated in tumors, causing immunotherapy resistance. Mechanistically, LTA4H deficiency prevents HNRNPA1 inhibition, promoting Ltbp1 mRNA maturation and subsequent TGF-β secretion. This drives CD206$^+$ macrophage polarization and liver damage, which is therapeutically reversed by combining anti-TGF-β and anti-PD-1 blockades [154]. In addition, other researchers have focused on Leukotriene B4 (LBT4); they found that ALOX5 expression in intrahepatic cholangiocarcinoma (ICC) cells drives M2 macrophage infiltration in the tumor microenvironment. Mechanistically, the ALOX5 metabolite LTB4 binds to BLT1/BLT2 on macrophages, activating the PI3K pathway to recruit them to tumor cells and promote progression [155]. In summary, leukotrienes, which represent another major class of eicosanoid lipid mediators, exert context-dependent but predominantly pro-tumoral effects on TAMs.

4. Specific Lipid-Associated Target of TAM in Cancer Therapy.

Given the central role of lipid metabolism in TAM-driven immunosuppression, each enzymatic node and signaling hub represents a potential therapeutic target. The following are the most promising categories.

4.1 CD36/FATP/LDLR (Lipid uptake)

The entry of exogenous lipids into TAMs is the first committed step in their metabolic reprogramming. Expressed in multiple cell types, the scavenger receptor CD36 participates in lipid uptake, immune

recognition, inflammatory responses, cell adhesion, and apoptosis [156-158]. It is a scavenger receptor for long-chain fatty acids, oxLDL, and oxidized phospholipids [159]. In pre-clinical models, blocking CD36 with neutralizing antibodies or small molecule inhibitors has been shown to reduce lipid droplet formation in TAMs, revert their phenotype to an M1-like state, and significantly suppress tumor growth and metastasis [36, 37, 160]. Moreover, CD36 is also expressed on tumor cells, and its inhibition may have dual anti-tumor effects. Moreover, nanoparticle-based delivery of anti-CD36 therapeutics to TAMs is an active area of research [161, 162]. Another target is the FATP (Fatty Acid Transport Proteins), particularly FATP2 (also known as SLC27A2), have also emerged as a key target. FATP2 is upregulated in TAMs and facilitates the uptake of lipids [163, 164]. Consequently, inhibitors of FATP2, such as Lipofermata, have been shown to reduce the accumulation of arachidonic acid and its subsequent conversion to PGE2, thereby blocking the downstream immunosuppressive cascade [164, 165]. In addition to fatty acid transporters, cholesterol uptake receptors represent another important axis. LDLR and SR-B1 (Scavenger Receptor Class B Type 1) are the primary receptors for cholesterol uptake from LDL and HDL particles [166-168]. In TAMs, these receptors are often upregulated to meet the high cholesterol demand for membrane synthesis and signaling [169, 170]. For example, targeting SR-B1, researchers developed M2-like TAM dual-targeting nanoparticles (M2NPs), whose structure and function were controlled by an α-peptide (SR-B1 targeting peptide) linked with M2pep (an M2 macrophage binding peptide) delivering anti-CSF-1R siRNA specifically to tumor-promoting M2-like macrophages. In melanoma-bearing mice, this approach depleted 52% of these macrophages and reduced tumor size by 87% [171].

4.2 FASN/SCD1/ACSL (Lipid biosynthesis and Fatty acid oxidation)

De novo lipogenesis, once considered negligible in non-adipose tissues, is highly active in pro-tumorigenic TAMs [172, 173]. FASN (Fatty Acid Synthase), the multi-enzyme complex that synthesizes palmitate from acetyl-CoA and malonyl-CoA, presents an actionable target across human carcinomas and pre-malignant lesions, offering a dual opportunity to metabolically starve tumors and reprogram the immune microenvironment [174-176]. Targeting FASN in TAMs, recently study revealed that DSS- or LPS-induced macrophage infiltration increases FASN and lipid levels, accelerating colorectal cancer growth in mice. Macrophage-secreted IL-6 drives this by activating STAT3 to upregulate USP14, which stabilizes FASN and promotes lipogenesis. Depleting macrophages or using 6-gingerol to inhibit USP14 successfully reverses these effects and suppresses tumor progression [177]. Moreover, MK1775 was identified as an agent that enhances anti-PD-1 efficacy by inhibiting the PI3K/AKT/mTOR pathway. This halts FASN-mediated fatty acid synthesis, suppressing fatty acid oxidation in TAMs. Concurrently, it triggers IRF-mediated CXCL10/CXCL11 secretion, promoting $CD8^+$ T cell infiltration to effectively block tumor progression through remodeled lipid crosstalk [178]. Targeting FASN or its regulatory pathways therefore holds promise not only for directly inhibiting tumor growth but also for reshaping the immunosuppressive lipid landscape and enhancing antitumor immunity.

SCD1 (Stearoyl-CoA Desaturase 1) is the rate-limiting enzyme that introduces a double bond into stearoyl-CoA and palmitoyl-CoA to produce oleoyl-CoA and palmitoleoyl-CoA, generating monounsaturated fatty acids (MUFAs), and plays an important role in cancer by promoting cell proliferation and metastasis [179-181]. It has been reported that TAM-secreted taurine suppresses ferroptosis in prostate cancer by activating the LXRα/SCD1 pathway. Cancer cells release miR-181a-5p-enriched extracellular vesicles that promote M2 macrophage polarization and taurine export via Lats1/Hippo/YAP signaling. This reciprocal feedback loop drives tumor therapeutic resistance by continuously inhibiting ferroptosis in the tumor microenvironment [182]. Inhibition of SCD1 leads to the accumulation of saturated fatty acids, which may cause the TAM phenotype from M2 to M1, restoring their ability to kill tumor cells and activate T cells [183].

ACSL (Acyl-CoA Synthetase Long-chain family) activates long-chain fatty acids to fatty acyl-CoAs, the first step before they can be oxidized or esterified into complex lipids. Across various malignancies, dysregulation of ACSLs creates an oncogenic dependence on metabolic reprogramming, impacting tumor progression, immune modulation, and therapy resistance, providing a rationale for developing anticancer therapeutics [184-186]. Notably, ACSL3 and ACSL4 are closely associated with ferroptosis [187]. Dysregulation of this enzyme can modulate cellular sensitivity to ferroptotic stimuli, thereby influenc-

ing tumor suppression and therapeutic responses. In TAM-related research, ACSL1 and ACSL4 are the two family members that primarily influence TAM fate [188-191]. For example, Low ACSL4 levels characterize nasopharyngeal carcinoma (NPC). Overexpressing ACSL4 or applying erastin triggers ferroptosis, increasing lipid peroxidation while suppressing NPC cell proliferation, invasion, and EMT. This axis additionally promotes anti-tumor M2-to-M1 macrophage polarization [191], and inhibitors like Triacsin C or small molecules targeting the ACSL1 active site can effectively block the rerouting of fatty acids away from oxidation and towards storage in lipid droplets, starving TAMs of the energy needed for their pro-tumor functions [188, 192].

Fatty acid oxidation (FAO) in the cancer TME fuels TAMs and T cells, promoting immunosuppressive phenotypes, T-cell exhaustion, and tumor progression under metabolic stress [193, 194]. CPT1A (Carnitine Palmitoyl transferase 1A) is the rate-limiting enzyme for the transport of long-chain fatty acyl-CoAs into the mitochondria for β-oxidation, which mediates TAM fate [123, 195, 196]. For example, Lei Ma et al. reported that Macrophage-derived L-carnitine interacts with CPT1A to drive ferroptosis resistance and $CD8^+$ T cell inactivation in lung cancer [123]. The compound Etomoxir is an irreversible inhibitor of CPT1A, and Etomoxir treatment has been shown to reduce the viability and M2 polarization of TAMs, enhance the efficacy of PD-1 blockade, and slow tumor growth [197-199].

In summary, the coordinated action of *de novo* lipogenesis, monounsaturated fatty acid synthesis, fatty acid activation, and fatty acid oxidation underpins the metabolic reprogramming of pro-tumorigenic TAMs. Targeting these pathways offers multiple opportunities to reprogram TAMs toward an anti-tumor phenotype, overcome therapy resistance, and enhance immunotherapeutic efficacy. Future strategies should focus on developing isoform-selective inhibitors and delivering them specifically to TAMs to maximize therapeutic benefit while minimizing off-tumor effects.

4.3 HMGCR/ACAT/CYP27A1 (Cholesterol metabolism)

Cholesterol homeostasis is a critical regulator of immune cell function. The role of cholesterol metabolism in regulating tumor biological processes, particularly oncogenic signaling pathways and the tumor microenvironment, has been extensively reported in recent years [129, 130, 200-202].

HMGCR (HMG-CoA Reductase), the rate-limiting enzyme of the mevalonate pathway, is a classic therapeutic target [203, 204], also as a novel target on TAMs. For instance, researchers have reported that eIF4E upregulates HMGCR to drive cholesterol synthesis, activating the XBP1/PD-L1 axis in macrophages. Inhibiting HMGCR successfully restores their antitumor activity, highlighting it as a therapeutic target to overcome tumor-driven immunosuppression [205]. Statins, which are HMGCR inhibitors, have pleiotropic effects that extend far beyond their canonical cholesterol-lowering function. In EGFR-driven lung adenocarcinoma, elevated epithelial GM-CSF secretion induces tumor-associated alveolar macrophage (TA-AM) proliferation. Driven by GM-CSF-PPARγ signaling, TA-AMs support tumor growth by fueling cholesterol efflux to cancer cells, which enhances EGFR phosphorylation. Inhibiting TA-AM PPARγ combined with statin therapy restricts cholesterol availability, suppressing tumor progression and boosting proinflammatory immunity [206].

CYP27A1 (Sterol 27-Hydroxylase) is a mitochondrial enzyme that converts cholesterol to 27-hydroxycholesterol (27-HC) [133, 207, 208]. In the TME, 27-HC produced by TAMs can promote tumor cell proliferation and suppress anti-tumor immunity. Inhibiting CYP27A1 with small molecules could reduce 27-HC levels, thereby elevating anti-tumor immunity.

4.4 SREBP1/2/PPAR

Targeting the transcription factors that orchestrate the entire lipid metabolic program offers a way to simultaneously block multiple downstream pathways [209-211]. SREBP1 (Sterol Regulatory Element-Binding Protein 1) is the master regulator of fatty acid synthesis, while SREBP2 regulates cholesterol synthesis and uptake [210, 212, 213]. Small molecule inhibitors of SREBP processing, such as Betulin, block the transport of SREBPs from the ER to the Golgi, preventing their cleavage and activation [214]. A recent study illustrates that PARP inhibitors enhance both anti- and pro-tumor macrophage features via SREBP-1-driven metabolic reprogramming. Combining PARP inhibition with CSF-1R blocking antibodies reprograms the tumor microenvironment, boosts $CD8^+$ T cell-mediated immunity, and extends

survival, offering a promising therapeutic strategy [215].

PPARs (Peroxisome Proliferator-Activated Receptors), especially PPAR-γ, are central to M2-like pro-tumorigenic polarization of TAMs by upregulating fatty acid oxidation polarization [216, 217]. For example, in S100A4$^+$ TAMs, IL-4 induces a protumor phenotype by upregulating PPAR-γ and CD36 to enhance fatty acid absorption and FAO [218]. While inhibition of the PPAR-γ pathway in TAMs constitutes a classic therapeutic strategy, several novel drugs exploiting this mechanism have been identified. Zhen-Yu Zhao et al. reported that (-)-Guaiol inhibits M2-type TAM polarization through PPAR-γ signaling, thereby suppressing lung cancer [219]. Moreover, Q11 inhibits M2 macrophage polarization by modulating the CYP2E1 / PPAR-γ axis, making CYP2E1 and Q11 potential therapeutic targets for HCC [220].

In summary, transcription factors SREBP1/2 and PPAR-γ serve as critical nodes controlling the lipid metabolic network in TAMs. These findings underscore that targeting master transcriptional regulators of lipid metabolism represents a promising and feasible avenue to overcome TAM-mediated immunosuppression and improve cancer immunotherapy outcomes.

Discussion and future direction

The compelling evidence reviewed herein establishes that lipid metabolic reprogramming is a cornerstone of TAM biology within the TME. Far from being a passive consequence of the lipid-rich environment, the alterations in lipid uptake, synthesis, oxidation, and signaling actively drive the functional polarization of TAMs toward immunosuppressive, pro-tumorigenic states. This discussion synthesizes the key findings, highlights unresolved questions, proposes a unifying hypothesis, and outlines future therapeutic directions.

One of the most significant insights from recent studies is the inadequacy of the classical M1/M2 paradigm for describing TAM metabolic states. As detailed in Section 2, single-cell technologies have unveiled a spectrum of lipid-associated TAM subpopulations. SPP1$^+$, TREM2$^+$, APOE$^+$, and FABP$^+$, each with distinct metabolic dependencies and functional roles. This heterogeneity suggests that effective therapeutic targeting will require precise subset-specific approaches rather than blanket modulation of lipid metabolism. A critical unresolved question is whether these TAM subsets represent distinct lineages, interchangeable states, or overlapping metabolic programs. Emerging evidence suggests that TAMs may transition between these states depending on local lipid composition, signaling cues, and disease stage. For example, while TREM2$^+$ TAMs are generally pro-tumorigenic in hepatocellular carcinoma and lung cancer, TREM2 deficiency in glioma models impairs phagocytosis and anti-tumor immunity, indicating context-dependent duality [50, 57, 63]. Similarly, FABP5 promotes anti-tumor IFN-β responses in one context yet drives immunosuppression in liver cancer [91, 92]. These opposing functions likely depend on the specific fatty acid ligands, upstream receptors, and downstream transcription factors engaged. Therefore, future studies must move beyond associative single-cell atlas studies and employ lineage-tracing and functional perturbation models to establish causality and context-specificity.

Another major theme is the instructive role of specific lipid-derived metabolites in dictating TAM fate. Long-chain fatty acids such as palmitic acid and oleic acid, cholesterol derivatives like oxysterols, sphingolipids including ceramides and S1P, and eicosanoids such as PGE_2 and leukotrienes all actively reprogram TAMs. Notably, the same metabolite can exert opposing effects depending on concentration, duration, and cellular context. For example, ceramide and palmitic acid together can switch macrophages from M2 to M1, suppressing epithelial-mesenchymal transition, whereas palmitic acid alone often drives immunosuppression via TLR4 signaling [112, 138]. PGE_2 is consistently pro-tumoral by impairing T cell bioenergetics, yet blocking its synthesis can restore anti-tumor immunity. These findings highlight the potential of targeting lipid-metabolizing enzymes or lipid-sensing receptors as immunotherapeutic adjuvants. However, given the systemic roles of these pathways in normal physiology, tissue-specific or TAM-targeted delivery systems will be essential to avoid on-target off-tumor toxicity.

From a therapeutic perspective, the landscape is rich with actionable nodes. Inhibitors of lipid uptake, *de novo* lipogenesis, FAO, and cholesterol metabolism have all shown preclinical efficacy in reprogramming TAMs and enhancing immune checkpoint blockade. However, several challenges remain. First, metabolic redundancy may allow TAMs to escape single-agent inhibition. Combination strategies may be required. Second, the impact of these agents on other immune cells and on tumor cells themselves must be carefully

evaluated, as both beneficial and detrimental effects have been reported. Third, the tumor-promoting or suppressing role of a given metabolic pathway can shift during tumor evolution and therapy, necessitating adaptive treatment regimens.

In conclusion, targeting lipid metabolism in TAMs represents a paradigm-shifting strategy in cancer immunotherapy. By moving beyond the M1/M2 dichotomy and embracing the complexity of lipid-associated TAM subsets, we can develop precision metabolic therapies that reprogram the TME, overcome immunotherapy resistance, and improve patient outcomes. The coming decade will likely witness the translation of these concepts from bench to bedside, with lipid-targeting agents entering clinical trials as part of combination immunotherapy regimens.

Author Contributions

JZ- Drafting and revising the manuscript. SJ- Assisted in drafting the manuscript. YW-Critically reviewing the manuscript. AQL- Critically reviewing the manuscript. PKFC- Critically reviewing the manuscript. JYCT- Critically reviewing the manuscript. RW- Critically reviewing the manuscript. DW- Concept Development, supervision, and critical review of the manuscript. CFN- Concept Development, critical review of the manuscript, and communication as the corresponding author.

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