Effects of glycolysis on the polarization and function of tumor-associated macrophages (Review)

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Abstract. Under conditions of oxygen sufficiency, tumor cells supply themselves with energy through glycolysis, which is one of the causes of their rapid proliferation, metastasis and acquisition of drug resistance. Tumor-associated macrophages (TAMs) are transformed from peripheral blood monocytes and are among the immune-related cells that constitute the tumor microenvironment (TME). Altered glycolysis levels in TAMs have an important impact on their polarization and function. The cytokines secreted by TAMs, and phagocytosis in different polarization states, affect tumorigenesis and development. Furthermore, changes in glycolysis activity of tumor cells and other immune-related cells in the TME also affect the polarization and function of TAMs. Studies on the relationship between glycolysis and TAMs have received increasing attention. The present study summarized the link between glycolysis of TAMs and their polarization and function, as well as the interaction between changes in glycolysis of tumor cells and other immune-associated cells in the TME and TAMs. The present review aimed to provide a comprehensive understanding of the effects of glycolysis on the polarization and function of TAMs.

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1. Introduction

Glycolysis is a respiratory metabolic pathway in cells that generates two molecules of ATP and pyruvate (1). When oxygen is available, pyruvate is oxidized by pyruvate dehydrogenase to produce acetyl coenzyme A (CoA), which enters the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) (2). When oxygen is absent, pyruvate is catalyzed by lactate dehydrogenase to lactic acid, which fuels the TCA cycle (3) and may also become a gluconeogenic precursor through gluconeogenesis (4). Tumor cells have been considered major consumers of glucose, producing lactic acid to fuel their growth through glycolysis, while generating nicotinamide-adenine dinucleotide phosphate through the parallel pentose phosphate pathway, despite the presence of oxygen (5,6). By contrast, the tumor microenvironment (TME) is the microecosystem in which the tumor survives and thrives, comprising tumor cells, stromal cells and associated immune cells, such as tumor-associated macrophages (TAMs), T cells and dendritic cells, as well as their products (e.g., cytokines and chemokines) (7). Macrophages are usually classified into classically activated macrophages (M1 type) and alternatively activated macrophages (M2 type) according to their activation and function (8). M1 macrophages are mainly energized by glycolysis, while the main source of energy for M2 macrophages is fatty acid oxidation and OXPHOS. Furthermore, in the presence of active OXPHOS, M2 type macrophage differentiation does not require glycolytic stimulation (9). Of note, recent studies have indicated that in the TME, TAMs consume

the most glucose (10), while interleukin (IL)-4-induced M2-like TAMs have significantly increased glycolytic reserves and the highest glycolytic capacity compared with those of resting macrophages (M0). M1-like TAMs further promote cancer metastasis and chemoresistance (11,12). This suggests that although M2-like TAMs are similar to M2 macrophages in terms of their differentiation characteristics and secretory factors, they exhibit a high dependence on glycolysis at the metabolic level (13).

During tumor development, TAMs infiltrating tumor tissues tend to exhibit high plasticity and undergo corresponding metabolic changes depending on oxygen and nutrient conditions, ultimately affecting their phenotype and function (14). Cytokines in the TME, including IL-12, tumor necrosis factor α (TNF-α) and interferon (IFN)-γ, promote macrophage polarization to the M1 state. When stimulated by IL-4 and colony-stimulating factor (CSF)-1 produced by cancer cells and $CD4^+$ T cells, as well as granulocyte macrophage (GM)-CSF produced by cancer cells, TAMs finally polarize to the M2 state (15-17). In the early stages of tumor development, TAMs tend to be the M1 type, while as the tumor progresses, the M2 type gradually predominates (18). The relationship between glycolysis and TAMs has received increasing attention and the purpose of the present review is to summarize the effects of alterations in the glycolytic process of TAMs on their polarization and function based on the progress of existing studies, as well as to summarize the role of tumor cells and immune cells in the body microenvironment in regulating the polarization and function of TAMs through glycolysis, to provide a comprehensive understanding of the relationship between glycolysis and TAMs.

2. Effects of altered glycolysis of TAMs on their own polarization and function

Effects of altered key glycolytic enzyme activities of TAMs on their polarization and function. When macrophages change from a quiescent to an activated state, the activities of key enzymes related to glycolysis are frequently altered. The regulation of kinases involved in glucose metabolism may alter the macrophage phenotype and affect cytokine production and the expression of key surface receptors (19). Among them, key enzymes of glycolysis, such as hexokinase (HK), phosphofructokinase (PFK) and pyruvate kinase M2 (PKM2), have important roles in the polarization and functional changes of TAMs (20-24).

HK. HK is the first rate-limiting enzyme of glycolysis, catalyzing the phosphorylation of glucose to glucose 6-phosphate and entering various downstream metabolic pathways (24). In mammals, five HK isozymes (HK1, HK2, HK3, glucokinase and HK domain containing 1) have been identified (25). Among them, HK1- and HK2-mediated glycolysis has a regulatory role in macrophage polarization. IFN regulatory factor 5 increases the expression of hypoxia-inducible factor-1α (HIF-1α) and actives HK1 through the activation of protein kinase B β, which in turn triggers M1 polarization of macrophages (26). However, in mouse J774A.1 macrophages, inhibition of mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), which affects HK1-dependent glycolysis, inhibited macrophage M1 polarization (27). In addition, in a study of HK2, it was found that the basic helix-loop-helix family member e40 promotes the activities of HK2 and PFK by increasing macrophage HIF1-α expression, further promoting macrophage polarization toward the M1 type (28). Studies have indicated that targeting HK activity using drugs effectively controls macrophage polarization and function. Increased levels of glucose transporter protein 1 (GLUT1), GLUT3 and HK2 in macrophages were revealed by western blot analysis after lipopolysaccharide (LPS) activation of RAW 264.7 macrophages (29), and targeted inhibition of HK2 by using the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) hindered macrophage polarization to M1 (30). In response to HK2, all-trans retinoic acid, a derivative of vitamin A, was found to promote IL-1β maturation and secretion by enhancing HK2 gene expression and the activation of NOD-like receptor thermal protein domain associated protein 3 inflammatory vesicles (31). Furthermore, in the gastric cancer TME, hypoxic conditions inhibited M1 by suppressing microRNA (miR)-30c expression and decreasing mTOR activity and glycolysis during TAM differentiation and function (32). Conversely, changes in M2 TAM glycolysis are closely related to their tumor-promoting function. In pancreatic ductal adenocarcinoma (PDAC), increased aerobic glycolysis promotes angiogenesis, extravasation and epithelial-mesenchymal transition, which was further supported by TAM polarization toward M2, whereas the use of the HK2 inhibitor 2-DG altered TAM glycolytic activity to reverse this function (33). Thus, HK2 has an important function in macrophage glycolysis, which also provides a new experimental basis to target and modulate HK2 to regulate the polarization state of TAMs and thus treat tumors.

PFK. PFK catalyzes the generation of fructose 6-phosphate to fructose 1,6-bisphosphate during glycolysis. Fructose-2,6-bisphosphate synthesized by PFK-2/fructose-2,6-bisphosphatase 3 (PFKFB3) is an allosteric activator of PFK, and it was found that GM-CSF upregulates macrophage glycolysis by enhancing PFKFB3 activity and ^{18}F-fluorodeoxyglucose uptake, promoting macrophage M1 polarization (34). After high glucose stimulation, bone marrow-derived macrophages polarize toward M1 and secrete inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines; however, silencing TGF-β activated kinase 1 binding protein 1 inhibited macrophage M1 polarization by affecting HIF-1α-mediated PFKFB3 activity to limit glycolysis in mice (35). Targeted knockdown of PFKFB3 to limit glycolysis flux also caused a decrease in NOS2 expression (36). Furthermore, after macrophage stimulation with TNF-α, two separate inhibitors were used to affect PFKFB3 activity, resulting in a significant reduction in glycolysis, along with significant inhibition of macrophage M1 polarization (22). By contrast, the anti-inflammatory drug dexmedetomidine affected HIF-1α binding to GLUT1, HK2 and PFKFB3 by downregulating HIF-1α expression to inhibit glycolysis and attenuate the LPS-induced pro-inflammatory response (37). Taken together, these results suggested that PFKFB3-mediated glycolysis has a key role in driving the activation of M1 macrophages (38), which may have implications for cancer therapy by modulating HIF-1α/PFKFB3-activated M1-type TAMs to influence tumor progression.

PKM2. PKM2 is an important pyruvate kinase that comes in two forms, with the pyruvate lyase activity of the tetrameric form of PKM2 being higher than that of the dimeric form (39).

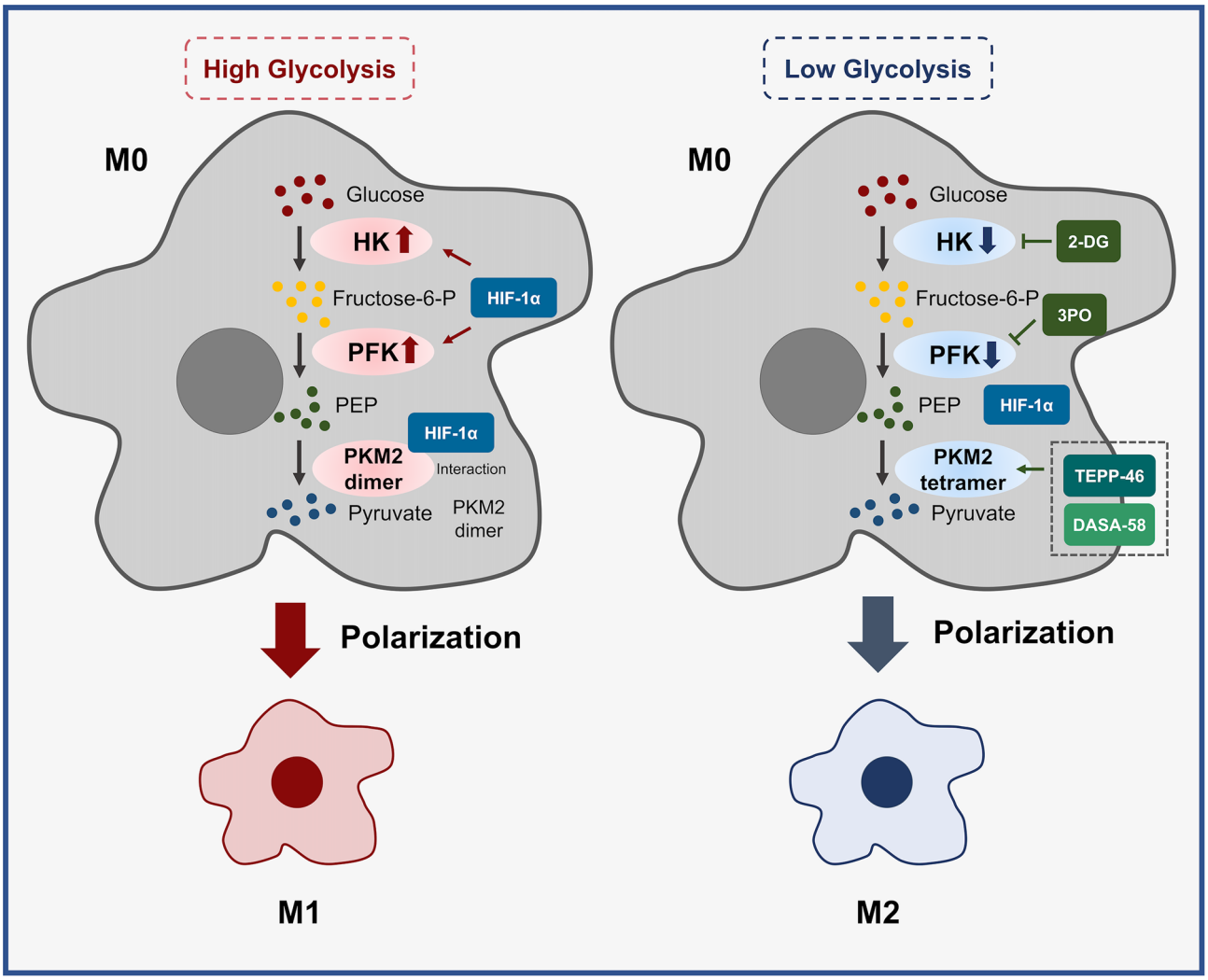

Figure 1. Effect of changes in the activity of key enzymes of TAM glycolysis on their polarization. When activated by external conditions, the activities of TAM key glycolytic enzymes, including HK, PFK and PKM2, were correspondingly upregulated, increasing the rate of glycolysis, while inducing the polarization of M0 TAMs to M1 TAMs. The corresponding downregulation of HK, PFK and PKM2 mediated low glycolytic activity and caused M2 polarization of TAMs. TAMs, tumor-associated macrophages; HK, hexokinase; PFK, phosphofructokinase; PKM2, pyruvate kinase M2; HIF, hypoxia-inducible factor; 2-DG, 2-deoxy-D-glucose; PEP, phosphoenolpyruvate.

The dimeric form of PKM2 may interact with HIF-1α in the nucleus and recruit hypoxia response elements by enhancing the binding of HIF-1α and p300, thereby promoting HIF-1α target gene activation, as well as macrophage M1 polarization (40). The use of small molecular activators DASA-58 and TEPP-46 to promote PKM2 tetramerization during LPS activation in mouse bone marrow-derived macrophages impaired the binding of PKM2 to HIF-1α and adversely affected macrophage M1 polarization (21). Furthermore, PKM2 serves as a physiological substrate for recombinant Sirtuin 5 (SIRT5) and the hyper-glycosylation mediated by SIRT5 deficiency may promote M1 polarization by promoting the conversion of PKM2 tetramers to dimers (41). Thus, PKM2-mediated glycolysis influences macrophage polarization toward the M1 type, and also has implications for targeting PKM2 structures in cancer therapy to regulate M1 TAMs. Furthermore, in the TME, TAMs are enriched in hypoxic regions and exhibit higher rates of glycolysis, and secrete immunosuppressive cytokines, while also upregulating growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), to induce angiogenesis to remodel and maintain tumor growth (42,43); furthermore, the key macrophage glycolytic enzyme PKM2 co-localized with F-actin in filopodia (44). Therefore, it may be speculated that glycolysis of TAMs has an important role in their migration to hypoxic regions.

In summary, altering the activity of key glycolysis enzymes has an impact on TAM polarization and function by mediating inflammatory vesicle formation, functional inflammatory factor secretion and immunosuppressive cytokine secretion (Fig. 1).

Effect of metabolic reprogramming of TAMs on their polarization and function. Cellular metabolic reprogramming is a major hallmark of cancer (45), which maintains tumor growth and proliferation. This leads to tumor cells no longer using the TCA cycle in mitochondria to produce ATP, but instead convert glucose to lactate via glycolysis (46). Even in the presence of oxygen, tumor cells still use the relatively low energy-producing efficiency of glycolysis to supply themselves

with energy (47). In immune cells, a similar metabolic pattern exists. Among macrophages, M1 macrophages activated by IFN-γ and LPS produced by type 1 T-helper cells (TH1) derive their energy from aerobic glycolysis, whereas M2 macrophages activated by TH2 cytokines IL-4 or IL-13 mainly depend on oxidative metabolism (13). In addition, the shift in the metabolic mode of TAMs from OXPHOS to aerobic glycolysis, induced by the TME, has an important impact on the induction of M1-like TAM activation (48). Taken together, it is clear that glycolysis-related metabolic reprogramming of macrophages has an important role in regulating their polarization.

Effects of glycolysis-related enzyme alteration-mediated metabolic reprogramming on the polarization and function of TAMs. During metabolic reprogramming, GLUT1 and pyruvate dehydrogenase kinase 1 (PDK1) in macrophages differentially affect glucose metabolism levels through the control of glucose flux and pyruvate, respectively (49,50).

Expression changes of GLUT1, which controls glucose transport and related enzymes in glycolysis, mediates the metabolic pathway shift to glycolysis (51). GLUT1 [also known as solute carrier family 2 member 1 (SLC2A1)] has a regulatory role in glucose flux and affects the process of macrophage glycolysis. After stable overexpression of GLUT1 in RAW264.7 macrophages, cellular bioenergetics analysis, metabolomics and radioactive tracer results indicated that overexpression of GLUT1 resulted in elevated glucose uptake and metabolism and increased levels of intermediates of the pentose phosphate pathway. Further detection of gene expression revealed elevated secretion of inflammatory mediators and polarization of macrophages toward the M1 type (52). Correspondingly, deletion of SLC2A1 in bone marrow-derived macrophages restricted glucose uptake, decreased macrophage glycolysis and the pentose phosphate pathway, and caused macrophage polarization toward the M2 type (53). HIF-1 is a heterodimeric transcription factor complex that includes two subunits: HIF-1α, which is responsive to O_2, and the constitutively expressed HIF-1β (26). HIF-1α induces the binding of GLUT1, which controls glucose transport, and related genes during glycolysis by forming a dimer with HIF-1β and the intranuclear hypoxia response element on the target gene (54). In aging skeletal muscle, HIF-1α downregulation inhibits its downstream GLUT1, affecting macrophage glycolysis, thereby inhibiting its M1 polarization and phagocytosis (55). In addition, the drug silver forgesine degrades the proteasome of HIF-1α by affecting the expression of GLUT1, PKM, PDK1, lactate dehydrogenase (LDH)A and PFK, which further inhibits macrophage glycolysis, thereby limiting their polarization to the M1 type (56). By contrast, monosodium urate and calcium pyrophosphate crystals mediate plasma membrane GLUT1 expression to promote macrophage glucose uptake and mediate metabolic reprogramming of aerobic glycolytic pathways to promote macrophage polarization toward the M1 type (57). However, it has also been suggested that, although the lack of GLUT1 attenuates glycolysis and the pentose phosphate pathway, macrophages are metabolically flexible enough, such that a lack of GLUT1 does not severely affect their activation status and function (54).

PDK1, a key regulatory enzyme in glucose metabolism, regulates the conversion of pyruvate to acetyl CoA during its entry into the TCA cycle. It was reported that the glycolysis activity induced by LPS activation of bone marrow-derived macrophages in mice was diminished due to PDK1 deficiency, with a corresponding increase in mitochondrial oxidative respiratory activity, which caused a conversion of macrophages from the M1 to the M2 type (20). Under hypoxia, HIF-1α enhances RAW 264.7 cell glycolysis and inhibits mitochondrial respiration by inducing PDK1-mediated metabolic reprogramming, preventing pyruvate from entering the TCA and converting it to lactate, which ultimately promotes M1 polarization (44). Of note, the detection of macrophages in mouse mammary tumor tissues by flow cytometry revealed that PDK1 deletion significantly inhibited the phosphorylation of protein kinase B (AKT) T308 and S6 in macrophages and suppressed the activation of AKT/mTOR signaling in TAMs. Further detection of related gene transcript levels revealed that PDK1 promoted the differentiation of M2-type macrophages (58).

Taken together, it is clear that metabolic reprogramming mediated by alterations in glycolysis-related enzymes GLUT1 and PDK1 has important implications for the polarization and function of TAMs.

Effect of the metabolic balance between glycolysis and OXPHOS on TAM self-polarization and function. During macrophage activation, LPS signaling mainly mediates protein Akt/mTOR enhancement of glucose uptake and promotes IL-10 and NO production, while NO inversely mediates OXPHOS and promotes a shift in metabolic direction toward glycolysis (59). In bone marrow-derived macrophages, SIRT3 deficiency promotes the macrophage M1 phenotype by shifting metabolism from OXPHOS to glycolysis (60). Fatty acid transport protein 1 affects macrophage metabolic reprogramming by controlling the activation of substrate metabolism, and its deletion enhances glycolysis (61). Recently, it was demonstrated that an iron-based metal-organic framework nanoparticle and an iron induce stimulated phagocytosis of tumor cells by macrophages through synergistic induction of mitochondrial alterations in TAMs, leading to a switch in their metabolic mode from mitochondrial OXPHOS to glycolysis, inducing TAMs to undergo M1 polarization (62). On the one hand, a clinically used Toll-like receptor 4 agonist, monophosphatidyl lipid A, facilitated the transition from OXPHOS to glycolysis by activating mTOR signaling (63); on the other hand, Metformin (Met) shifted the state of TAMs to the M1 type by targeting and inducing a decrease in OXPHOS while increasing glycolysis (64). A *Pseudomonas aeruginosa* protein, PcrV, increased glycolytic activity and promoted the conversion of TAMs to the M1 type by activating the PI3K/AKT/mTOR signaling pathway, and the resulting increase in nitric oxide-related cytotoxicity induced Lewis lung carcinoma cell apoptosis (65). Furthermore, the anti-malarial drug chloroquine promotes the reprogramming of TAM metabolism from OXPHOS to glycolysis by increasing the lysosomal pH of macrophages, releasing Ca^{2+} through the lysosomal Ca^{2+} channel mucus-1, inducing the activation of p38 and NF-κB, and activating transcription factor EB (TFEB), which in turn polarizes TAMs from the M2 to the anti-tumor M1 phenotype (66). In addition, K^+ in tumors inhibits the anti-tumor ability of TAMs. Among them, Kir2.1 has an important molecule in ion balance and its deletion causes the metabolism of TAMs to shift from oxidative phosphorylation to glycolysis, leading to the reactivation

of TAMs' immune function, which is not conducive to tumor growth. Kir2.1 is an important and potential therapeutic target for restoring the anti-tumor ability of TAMs (67). Research has indicated that a SnSe nanosystem modeled using LDH may achieve M1 macrophage activation and restore its anti-tumor function by altering the tumor microenvironment and reprogramming the metabolic mode of TAMs from OXPHOS to glycolysis (68). By contrast, a novel supramolecular nanotherapeutic reprograms TAMs from the M2 type to the M1 type by inhibiting the TCA cycle and upregulating glycolytic metabolism, while significantly affecting phagocytic function (69).

In contrast, the glycolysis inhibitor 2-DG induced a shift in macrophage energy metabolism from glycolysis to OXPHOS by upregulating p-AMPKα levels and inhibiting NF-κB activation (70,71). Upregulation of arginase 1 (ARG1) expression levels with a corresponding downregulation of iNOS expression was reported, which promoted the bioenergy of macrophages and suggested conversion of macrophages to the M2 type. Metabolomic assays suggested an increase in glycolysis and pentose phosphate pathway metabolites, such as those of lactate, glyceraldehyde 3-phosphate, glycerol-3-phosphate biosynthesis, 3-phosphoglycerate, 2,3-diphosphoglycerate, fructose 1,6-bisphosphate, glucose-6-phosphate, fructose-6-phosphate and phosphoenolpyruvate during macrophage activation; and a corresponding decrease in mitochondrial oxidation products, such as fumarate, succinate, citrate and isocitrate (72). Furthermore, downregulation of HIF-1α inhibited glycolysis after overexpression of miR-223 in RAW264.7 cells, enhanced mitochondrial respiration and promoted M2 polarization (73). In addition, downregulation of glycolysis mediated by both mTOR and HIF-1α attenuated IgG immune complex-induced M1 macrophage activation *in vitro* (74). This suggested that HIF-1α may affect its own polarization and function by regulating macrophage metabolic reprogramming and stimulating the shift from OXPHOS to glycolysis. Of note, the β2 receptor agonist (R)-salbutamol inhibited macrophage M1 polarization by reducing aerobic glycolysis and enhancing mitochondrial respiration (75). By contrast, GM-CSF, an upstream activator of mTORC2 in the pathway involving PI3K and AKT, promotes M2 polarization by reducing glycolysis and increasing fatty acid oxidation and OXPHOS (11). Furthermore, under IL-4 activation, the IL-33/ST2 axis regulates mitochondrial phagocytosis levels by affecting mTOR activity, causing a metabolic switch from OXPHOS to glycolysis in TAMs, further increasing the expression of M2 polarization-related genes and ultimately promoting tumor growth (76). Changes in the external environment also alter the polarization state and functions of TAMs by affecting their metabolic balance; it has been indicated that gut microbiota metabolites short chain fatty acids induce a shift in intestinal macrophage metabolism from glycolysis to OXPHOS, and further use of antibiotics upregulates the expression of genes involved in glycolysis, but not by inducing phosphorylation of the mTOR signaling pathway. In turn, enhanced metabolic functions of colonic macrophages include increased extracellular acidification rate and oxygen consumption rate (77). In addition, studies have indicated that after near-infra red irradiation of THP-1 cells, the activity of citrate synthase, a key enzyme in the tricarboxylic acid cycle, was obviously upregulated due to H3K4 trimethylation at the promoter region (78), which would cause metabolic reprogramming of macrophages, metabolic shift from glycolysis to TCA and OXPHOS, and then cause macrophage to M2 type polarization (79). Furthermore, deletion of the glucose-6-phosphate transporter gene inhibited glycolysis and increased mitochondrial OXPHOS, and is a cause of M1 macrophage suppression (80).

However, data from a proteomic analysis indicated that the expression of TAM glycolysis-related genes, such as that encoding HK2, and those encoding the downstream proteins phosphofructokinase-1 liver type and α-enolase, were significantly upregulated during breast cancer induction (81). Furthermore, the use of 2-DG significantly inhibited the expression of the M2 marker IL-10 in TAMs induced by hepatocellular carcinoma (HCC) regulatory mediators under normoxic conditions (82). This suggested that glycolysis in TAMs is not exclusively triggered by hypoxic stress stimuli and that this reprogramming of glycolytic metabolism may have an important role in the differentiation of TAMs, while signaling molecules from tumor cells may promote TAM glycolysis and maintain their M2 phenotype under normoxic conditions. Transcriptomic and metabolic analyses revealed that in mouse and human lung tumors, TAMs gradually exhibit higher oxidative metabolism and glycolysis, while lactate generated by glycolysis serves as an additional carbon source to support their oxidative metabolism, causing an upregulation of ARG1 expression, and suggesting a gradual polarization of M1 macrophages to the M2 type (83). Even MV3 human melanoma cell-stimulated generation of M2 TAMs requires only glycolysis, without the participation of the pentose phosphate pathway or fatty acid oxidation (13), whereas activation of the Wnt2b/β-catenin/c-Myc signaling pathway enhances the expression of key glycolytic enzymes, including HK2, PKM2, LDHA and LDHB in HCC-derived TAMs and promotes their M2 polarization (82). IL-13 extracted from the gastric cancer cell line MKN45 not only induced elevated M2-type markers CD163, IL-4 and IL-13 in macrophages, but also activated the expression of glycolysis-related enzymes, including GLUT3, glycosylphosphatidylinositol, phosphoglycerate kinase 1, LDHA, PFKFB3 and HK2, promoting upregulation of glycolytic activity, while assays indicated that this change was associated with TAM amino acid metabolism and fatty acid metabolism independently (84).

In summary, the altered metabolic balance between glycolysis and OXPHOS affects the polarization and function of TAMs (Fig. 2).

3. Effects of altered levels of glycolysis in tumor cells and other immune cells in the TME on TAM polarization and function

Effects of altered levels of tumor cell glycolysis on TAM polarization and function. Unlike normal cells, tumor cells convert glucose into lactic acid through aerobic glycolysis to maintain growth and biosynthesis; this process is known as the Warburg effect. First, with the participation of GLUT1, glucose is transported into the cell, where pyruvate is generated under the action of key glycolytic enzymes, including HK, PKF and PKM. Further, lactate is generated under the catalysis of LDHA and transported out of the cell by monocarboxylic acid transporter 4 (MCT4) and then enters the tumor microenvironment (77).

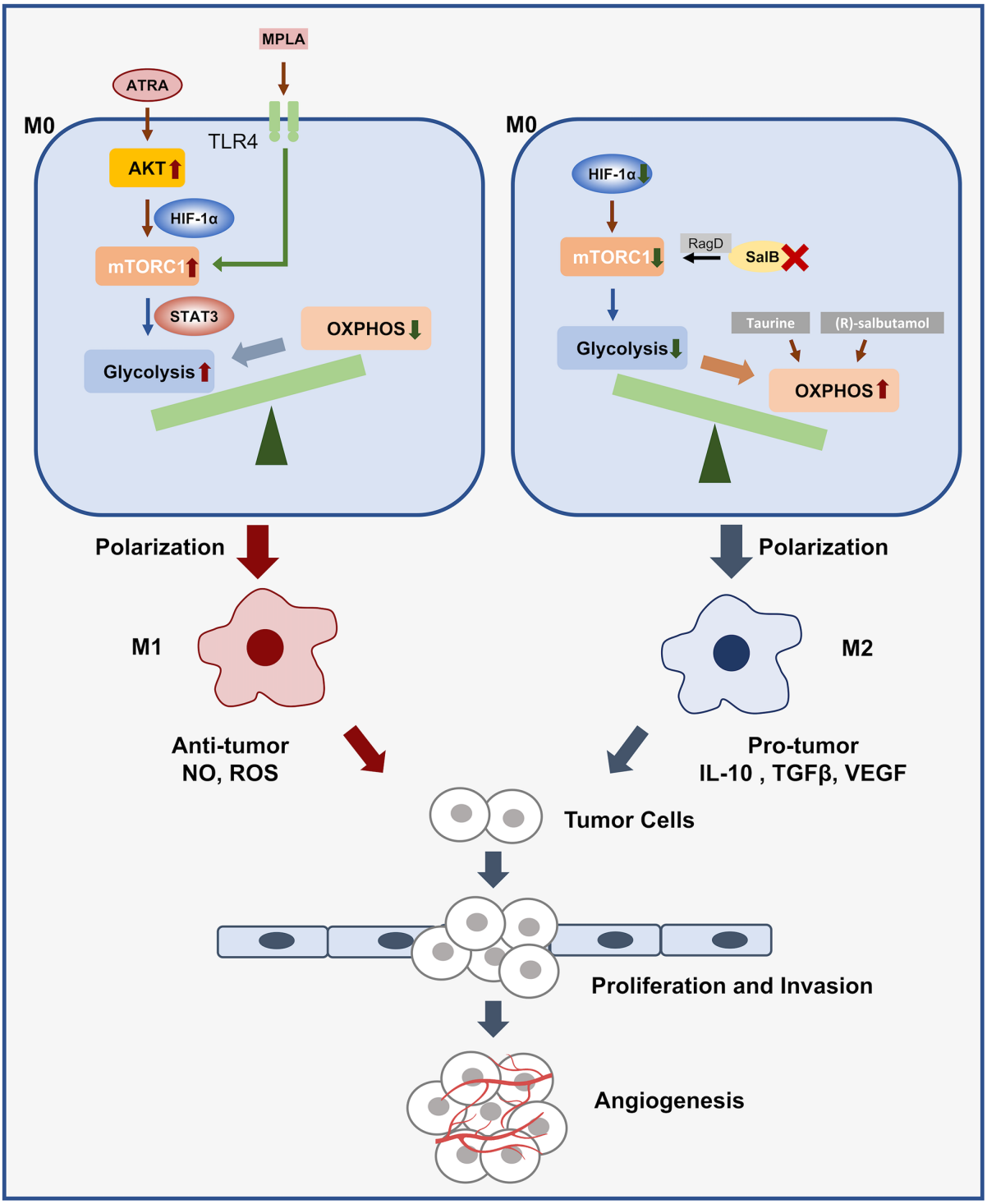

Figure 2. Effect of changes in the metabolic balance of glycolysis and OXPHOS on the polarization and functions of tumor-associated macrophages. In the left panel, upregulation of glycolytic activity of TAMs mediated by AKT/mTORC1/STAT3 promoted a shift in their metabolic direction from OXPHOS to glycolysis, while activation of mTOR signaling using TLR4 agonist-monophosphoryl lipid A also promotes a shift from OXPHOS to glycolysis in TAMs, which favors their polarization toward the M1 type and then exert anti-tumor functions through the production of NO and ROS. By contrast, the right panel shows that downregulation of glycolytic activity mediated by HIF-1α/mTORC1 downregulation caused a metabolic shift of TAMs toward OXPHOS and eventually toward M2 polarization. In addition, the use of the drugs Taurine and (R)-salbutamol promoted TAM transformation toward M2-type polarization by enhancing OXPHOS activity. Meanwhile, tumor-promoting M2 TAMs cause proliferation and invasion of tumor cells and further angiogenesis through the production of IL-10, TGF-β and VEGF. TLR, Toll-like receptor; ATRA, all-trans retinoic acid; TAMs, tumor-associated macrophages; HIF, hypoxia-inducible factor; STAT3, signal transducer and activator of transcription 3; NO, nitric oxide; ROS, reactive oxygen species; mTORC1, mammalian target of rapamycin complex 1; MPLA, monophosphatidyl lipid A; OXPHOS, oxidative phosphorylation.

In the Warburg effect, tumor cells release large amounts of lactate via glycolysis, causing metabolic reprogramming of stromal cells, including cancer-associated fibroblasts (CAFs) and TAMs (85), which undergo aerobic glycolysis and produce metabolites to promote tumor progression, while impeding the function of immune cells in the TME and promoting

immune escape of tumors (86). Tumor-derived lactate induces glycolysis signaling of TAMs to further polarize them toward the M2 type to promote tumor immune escape; however, TAM-derived lactate promotes tumor progression while supporting tumor energy metabolism as a signaling molecule and fuel for the TCA cycle (87-90). Thus, the lactate-mediated interaction between tumor cells and TAMs is a reciprocal process. In this process, tumor-derived lactate mediates polarization and functional changes in TAMs through two signaling pathways, the MCT-mediated signaling pathway and the G protein-coupled receptor-mediated signaling pathway. Among them, MCT1 deletion blocks M2 polarization (91). Numerous studies have indicated that in the TME, glycolysis of TAMs and activation of HIF-1α promote each other, and together they induce the M2 phenotype of TAMs. Lactate, produced by tumor cell glycolysis, has a key signaling function by mediating the induction of ARG1 and VEGF expression in TAMs by HIF-1α and promoting M2 polarization of TAMs, which is independent of the acidic microenvironment (92,93). Furthermore, in gastric cancer, tumor-derived lactate is able to promote TAM polarization toward the M2-type by activating the MCT-HIF-1α pathway (94) and increasing their infiltration (95). miR-3679-5p, delivered to lung cancer cells via M2 macrophage exosomes, downregulates E3 ligase neural precursor cell-expressed developmentally down-regulated 4-like expression, thereby stabilizing tumor cell c-Myc and leading to elevated glycolysis activity, and the resulting high lactate production induces M2 to M1 conversion of macrophages via HIF-1α (96). Furthermore, lactate activates MCT-mediated mTORC1, leading to phosphorylation and inactivation of the downstream TFEB, which further inhibits the expression of ATP6V0d2; however, blockade of ATP6V0d2 in macrophages leads to activation of HIF-2α, which in turn promotes M2 polarization and VEGF expression, further contributing to their angiogenic function (97). In contrast, in breast cancer, zinc finger E-box binding homeobox 1 induces glycolytic activity in tumor cells through the PI3K/Akt/HIF-1α signaling axis and further lactate production stimulates the protein kinase A/cAMP-responsive element binding protein signaling pathway in TAMs to induce their differentiation toward the M2 phenotype (98). Furthermore, in pituitary adenomas, lactate further promotes tumor invasion by activating mTORC2/Akt signaling and promoting the M2 polarization of TAMs (99). In head and neck squamous cell carcinoma, high levels of lactate stimulate the expression of CD163, a marker of M2 macrophages. Of note, the lactate concentration in the TME was negatively correlated with CD68 expression, but positively with CD163 expression, implying that lactate decreases the migratory capacity of macrophages (99). A study on pancreatic ductal adenocarcinoma found that vascular cellular adhesion molecule-1 (VCAM-1) mediates a shift in tumor cell metabolism to aerobic glycolysis, which increases lactate production and thus promotes M2 polarization of macrophages, while TAM C-C motif secretion of chemokine ligand 18 (CCL18) mediates the upregulation of VCAM-1 in PDAC and promotes the malignant progression of tumor cell migration and invasion *in vitro* (100).

In addition, lactate may affect TAM-related functions by mediating HIF-1α, including involvement in tumor immunosuppression, drug resistance and angiogenesis. A study of cervical cancer indicated that lactate secreted via aerobic glycolysis of tumor cells upregulated HIF-1α expression, inhibited NF-κB activation and further promoted IL-1β, IL-10 and IL-6 secretion (101). In addition, glioma-derived exosome miR-1246 then activates the STAT3 signaling pathway and inhibits NF-κB signaling pathway-induced M2 macrophage polarization by targeting telomeric repeat-binding factor 2 interacting protein, thus promoting the formation of an immunosuppressive microenvironment (102). Meanwhile, in tamoxifen-resistant estrogen receptor-positive breast cancer, tumor cells highly express a sodium/glucose cotransporter (SGLT1) to promote glycolysis, releasing large amounts of lactic acid into the TME. In turn, these lactates increase epidermal growth factor secretion by activating HIF-1α/STAT3 signaling in TAMs, which in turn promotes SGLT1 expression in tumor cells. This process creates a positive feedback loop between tumor cells and TAMs, a cycle that promotes tamoxifen resistance (103). Furthermore, lactate activation of human macrophages to the TAM phenotype simultaneously affects Notch signaling in macrophages to stimulate CCL5 secretion. In turn, CCL5 promotes aerobic glycolysis in breast cancer cells via AMPK signaling, thus forming a metabolic feedback loop (104). The above studies suggested that lactate induces M2 polarization and enhances the tumor-promoting function of TAMs through the MCT1/HIF-1α signaling pathway.

Therefore, certain studies have also focused on immunotherapy induced by amplified immunogenic cell death (ICD). It was demonstrated that the use of a regulator, panobinostat, which induces histone acetylation in tumor cells, effectively inhibited the glycolysis of tumor cells, resulting in a decrease in lactate, ultimately causing the transformation of TAMs into anti-tumor M1 types (105). In addition, the biomimetic nanosystem designed by Wang *et al* (106) effectively inhibits tumor growth by consuming lactate in the TME, finally causing TAMs to polarize from M2 to M1. Furthermore, a nanoscale mutagen sensitive to reactive oxygen species (ROS) initiates tumor-specific effector T-cell infiltration by inducing ICD depletion of TAMs, thereby activating an anti-tumor immune response, which suggests the feasibility of immunotherapy methods that mediate tumor cell glucose metabolism and lactic acid-induced ICD (107). In addition, the use of mannose may have a synergistic inhibitory effect on glycolysis in TAMs and cancer cells, leading to cell apoptosis and inducing systemic anti-tumor immune responses (108). The synergistic action with radiotherapy may effectively inhibit tumors and their metastasis.

In summary, altered levels of tumor cell glycolysis affect the polarization and function of TAMs (Fig. 3); it also provides a new perspective for indirect immunotherapy targeting glycolysis and lactate production in tumor cells.

Effects of altered fibroblast glycolysis levels in the TME on TAM polarization and function. CAFs are the most abundant stromal cells in the TME, and in addition to their important role in tumorigenesis and development, CAFs regulate the TME (109). CAFs secrete IL-6, M-CSF, monocyte chemoattractant protein-1 and stromal cell-derived factor-1, which promote macrophage infiltration and differentiation (110). Furthermore, unlike normal breast-derived fibroblasts, CAFs isolated from human breast cancer may promote the differentiation of monocytes into M2 macrophages (111). This differentiation is evident in terms of functional and phenotypic characteristics

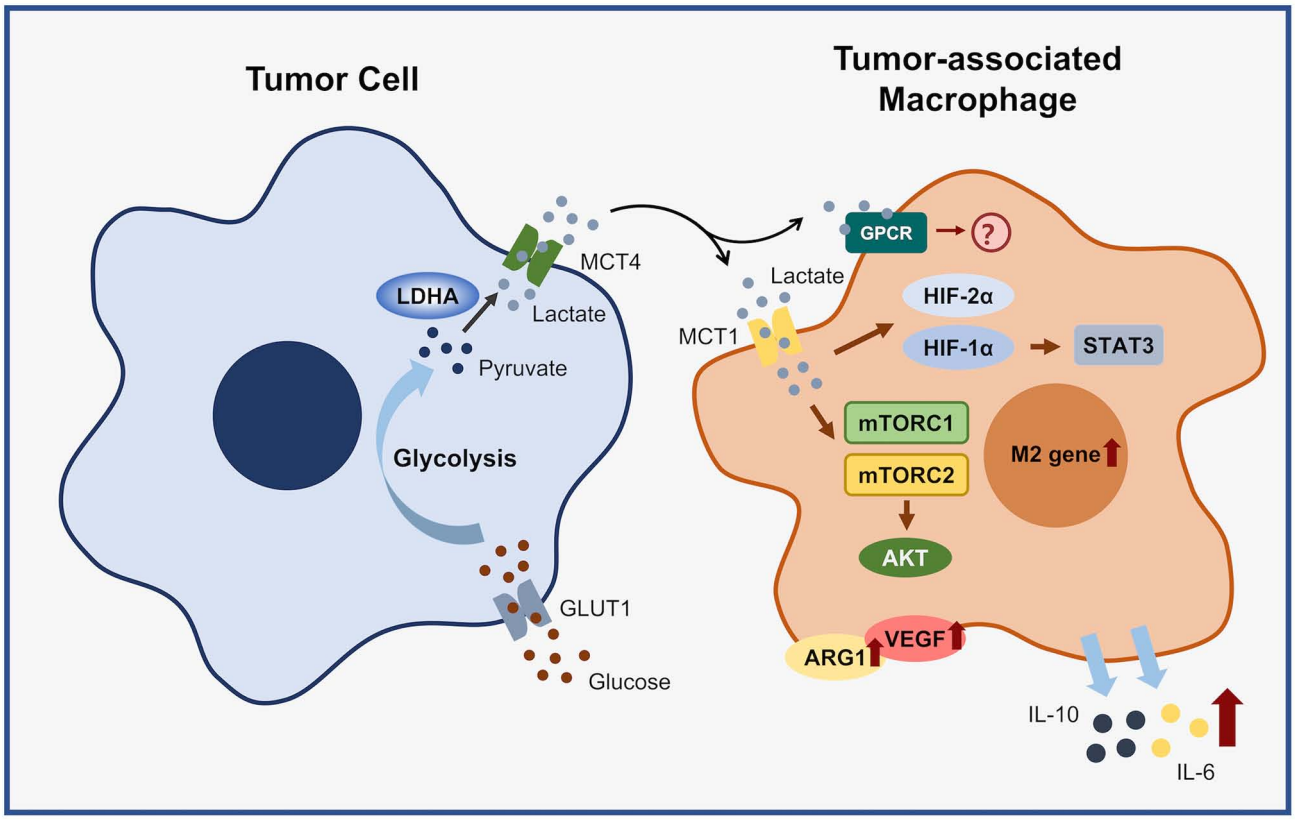

Figure 3. Effect of lactate, a glycolytic product of tumor cells, on the polarization and function of TAMs. Glucose enters tumor cells via GLUT1 and generates pyruvate via glycolysis, which is further converted to lactate via LDHA. Intracellular lactate is transported into the TME via MCT4 and into TAM cells via MCT1 on the surface of TAMs, causing upregulation of HIF-1α and HIF-2α, and mTORC1 and mTORC2 expression, further activating STAT3 and AKT, which induces M2-type gene expression. This results in elevated levels of VEGF and ARG1 on the surface of TAMs as well as increased secretion of IL-6 and IL-10, further promoting tumor growth. HIF, hypoxia-inducible factor; TAMs, tumor-associated macrophages; TME, tumor microenvironment; STAT3, signal transducer and activator of transcription 3; mTORC1, mammalian target of rapamycin complex 1; LDHA, lactate dehydrogenase A; GLUT1, glucose transporter protein 1; MCT4, monocarboxylic acid transporter 4; ARG1, arginase 1; GPCR, G protein-coupled receptor.

of pulmonary myofibroblasts after metabolic reprogramming-mediated upregulation of glycolysis to produce lactate, which indirectly regulates macrophage polarization (112). In addition, pulmonary myofibroblasts were induced by TGF-β1, glycolysis was upregulated, lactate was significantly increased and the expression of fibrogenic mediators in macrophages was promoted. Lactate also induced histone emulsification of the profibrotic gene (ARG1 and PDGFA) promoter in macrophages, triggering M1 polarization (112). In addition, CAFs exhibited greater glucose uptake, lactate production and elevated expression of LDHA, PKM2 and miR-21 compared with normal fibroblast. miR-21 inhibition decreased the degree of glycolysis in CAFs. The OXPHOS and invasive capacity of pancreatic cancer cells were decreased after co-culture with miR-21 inhibitor-CAFs (113), which provided new evidence for possible crosstalk between CAFs and TAMs.

Impact of altered lymphocyte glycolysis levels in the TME on TAM polarization and function. Lymphocytes generally include T lymphocytes, B lymphocytes and natural killer cells. Based on their surface CD molecules, T lymphocytes may be divided into various subpopulations. It has been indicated that Met promotes ROS production and increases glycolysis in the mitochondria of tumor-infiltrating $CD8^+$T lymphocytes (CD8TIL) by activating ROS, which in turn leads to IFN-γ secretion by promoting CD8TIL proliferation (114), while CD36 deficiency impairs oxidized low-density lipoprotein-stimulated monocyte-derived macrophage NF-κB production, thereby downregulating macrophage expression of pro-inflammatory factors IL-1 receptor antagonist, IL-1β, IL-6, TNF-α and IFN-β (115). When propranolol, a pan-β receptor blocker, or mice deficient in β2-adrenoceptors (β2-AR) were used, blockade of β-AR signaling increased glycolysis and OXPHOS in tumor-infiltrating lymphocytes, resulting in increased expression of the effector molecules IFN-γ, granzyme B and IL-12A and associated pro-inflammatory cytokines (IL-1B, IL-4, IL-6 and IL-10) expression was reduced (116). Although there are relatively few studies on the regulation of macrophage polarization and function via lymphocyte glycolysis, they offer certain possibilities to influence macrophage-related functions by altering the lymphocyte glycolytic regulation of the TME.

Effects of altered levels of myeloid-derived suppressor cells (MDSCs) and adipocyte glycolysis in the TME on TAM polarization and function. In adipose tissue, macrophage exposure to the saturated fatty acid palmitate triggers an upregulation of HIF-1α that increases glycolysis and ultimately leads to IL-1β production (117). Death of pseudohypoxic adipocytes initiates macrophage pro-inflammatory translation, and atherosclerotic injury associated with abnormal lipid metabolism also shifts

macrophages from the M2 to the M1 type (118). These studies suggested that when macrophages are in adipose tissue, the hypoxic environment induces macrophage glycolysis and polarization toward the M1 type, which also provides ideas for inflammation therapy (117,118).

Bone MDSCs accumulate in tumors and peripheral lymphoid organs and are divided into neutrophils polymorphonuclear MDSCs and monocyte MDSCs (M-MDSCs), which have a role in the TME and TAMs. The difference is caused by the CD36-mediated dependence of tumor-associated MDSCs on fatty acid oxidation as their main energy source. Under hypoxic conditions, activation of HIF-1α induced a shift in MDSC metabolic mode from OXPHOS to glycolysis, while HIF-1α promoted the differentiation of M-MDSCs toward TAMs by downregulating CD45 and STAT3 activity (119). In addition, bone marrow MSC-derived exosomes mediate glycolysis by inhibiting HIF-1α, downregulating the expression of glycolytic essential proteins and preventing LPS stimulation of M1 polarization-induced inflammation (120).

4. Problems and perspectives

Altered key glycolysis enzyme activity in TAMs affects their own polarization and function. Furthermore, the effects of metabolic reprogramming on the polarization and function of TAMs have been intensively studied. In addition, altered levels of glycolysis in tumor cells and other immune cells in the TME have an important role in TAM polarization and function. Although the effect of changes in glycolysis activity mediated by altered activities of key enzymes in TAMs on their polarization status and function has been investigated, whether kinase changes directly affect the polarization and function of TAMs, as well as the underlying mechanisms, remain to be determined. Furthermore, studies have indicated that the metabolic homeostasis between glycolysis and OXPHOS has an important role in the polarization and function of TAMs, providing theoretical support for the search for targeted therapeutic pathways. In the TME, lactate, a glycolysis metabolite of tumor cells, induces the development of a pro-tumor phenotype in TAMs, which also suggests that other metabolites of tumor cells, including succinate, may have a regulatory role in TAM polarization and function. These observations prompted us to hypothesize that there is a competitive relationship between tumor cells and TAMs for the uptake of glucose in the microenvironment. Therefore, the study of the mechanism of the interaction between glycolysis and tumor-associated macrophage polarization and function may further clarify their intrinsic connection and provide new perspectives for targeted therapy.

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Authors' contributions

JC wrote the manuscript and drew the figures. FZ and SL performed the literature search and contributed to manuscript revision. LC and YZ designed the study and revised the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors have no competing interests to declare.

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