Metabolic reprogramming in the immunosuppression of tumor-associated macrophages

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Abstract

Tumor-associated macrophages (TAMs) are an essential proportion of tumor-infiltrating immune cells in the tumor microenvironment (TME) and have immunosuppressive functions. The high plasticity and corresponding phenotypic transformation of TAMs facilitate oncogenesis and progression, and suppress antineoplastic responses. Due to the uncontrolled proliferation of tumor cells, metabolism homeostasis is regulated, leading to a series of alterations in the metabolite profiles in the TME, which have a commensurate influence on immune cells. Metabolic reprogramming of the TME has a profound impact on the polarization and function of TAMs, and can alter their metabolic profiles. TAMs undergo a series of metabolic reprogramming processes, involving glucose, lipid, and amino acid metabolism, and other metabolic pathways, which terminally promote the development of the immunosuppressive phenotype. TAMs express a pro-tumor phenotype by increasing glycolysis, fatty acid oxidation, cholesterol efflux, and arginine, tryptophan, glutamate, and glutamine metabolism. Previous studies on the metabolism of TAMs demonstrated that metabolic reprogramming has intimate crosstalk with anti-tumor or pro-tumor phenotypes and is crucial for the function of TAMs themselves. Targeting metabolism-related pathways is emerging as a promising therapeutic modality because of the massive metabolic remodeling that occurs in malignant cells and TAMs. Evidence reveals that the efficacy of immune checkpoint inhibitors is improved when combined with therapeutic strategies targeting metabolism-related pathways. In-depth research on metabolic reprogramming and potential therapeutic targets provides more options for anti-tumor treatment and creates new directions for the development of new immunotherapy methods. In this review, we elucidate the metabolic reprogramming of TAMs and explore how they sustain immunosuppressive phenotypes to provide a perspective for potential metabolic therapies.

Keywords: Immune checkpoint inhibitors; Immunosuppression; Metabolism; Tumor-associated macrophages; Tumor microenvironment

Introduction

Peripheral blood and tissue resident tumor-associated macrophages (TAMs) constitute a tremendous segment of infiltrating myeloid cells in the tumor microenvironment (TME) of most malignant solid tumors. Importantly, TAMs display proangiogenic properties.[1-4] According to environmental perturbations, macrophages differentiate into two classes: anti-tumor M1-phenotype and pro-tumor M2-phenotype macrophages. The latter resemble TAMs. These two types of macrophages have their own metabolic profiles, which are adapted to their functions.

In terms of glucose metabolism, pro-inflammatory M1-like macrophages show an enhancement in glycolytic metabolism and the pentose phosphate pathway (PPP), whereas the tricarboxylic acid (TCA) cycle is impaired and mitochondrial oxidative phosphorylation (OXPHOS) is attenuated. However, anti-inflammatory M2-like macrophages elevate OXPHOS and diminish PPP. Both M1- and M2-like macrophages potentiate fatty acid synthesis. Furthermore, M1-like macrophages generate nitric oxide from L-arginine by expressing inducible nitric oxide synthase (iNOS), while anti-inflammatory M2-like macrophages harness arginase 1 (Arg-1) to metabolize L-arginine; glutamine metabolism is also increased in M2-like macrophages.[5] Therefore, the metabolic reprogramming that occurs in TAMs with tumor-promoting effects (similar to those of M2-like macrophages) has been extensively studied, and it has been discovered that TAMs metabolic

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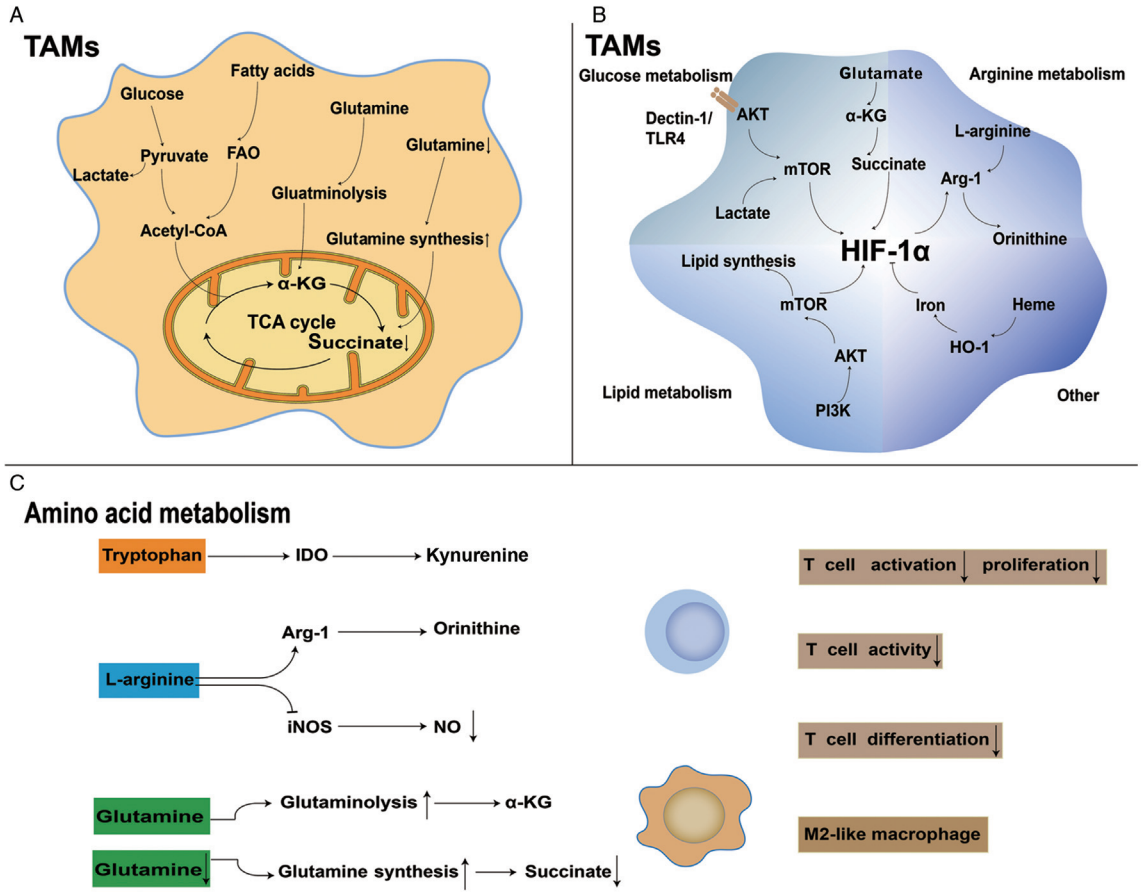

Figure 1: Metabolic reprogramming of tumor-associated macrophages (TAMs). (A) TAMs use glucose, lipids, and glutamine to enter the tricarboxylic acid cycle and produce ATP as energy source. (B) Relationship between metabolism and HIF-1α: mTOR is important for the transcription of HIF-1α. In addition, acidic and hypoxic tumor microenvironment (TME) can stimulate HIF-1α expression. Succinate, a glutamine metabolite, may partially respond to HIF-1α; whereas HIF-1α can affect the expression of Arg-1, affecting L-arginine metabolism. An excessive accumulation of intracellular iron inhibits HIF-1α activation. (C) Amino acid metabolism reprogramming in TAMs. TAMs upregulate IDO and Arg-1, increasing ornithine and kynurenine production and reducing the NO level, which have inhibitory effects on T cells. The α-ketoglutarate (α-KG) produced by glutaminolysis is beneficial for maintaining the M2-like phenotype. However, when intracellular concentrations of glutamine are low, the corresponding decrease in succinate also contributes to the immunosuppressive function of M2-like TAMs. Arg-1: Arginase 1; AKT: Protein kinase B; CoA: Coenzyme A; α-KG: α-ketoglutarate; FAO: Fatty acid beta-oxidation; HIF-1α: Hypoxia-inducible factor-1α; HO-1: Heme oxygenase-1; IDO: Indoleamine 2,3-dioxygenase; iNOS: Inducible nitric oxide synthase; mTOR: Mammalian target of rapamycin; NO: Nitric oxide; PI3K: Phosphatidylinositol-3-kinase; TCA: Tricarboxylic acid; TLR4: Toll-like receptor 4.

reprogramming is intimately related to the properties of the tumor cells.

The rapid proliferation of tumor cells leads to altered metabolites in the TME, such as glucose starvation and lactate accumulation; metabolite level modifications, in turn, contribute to the metabolic reprogramming of TAMs, as metabolites can act as signaling molecules to hijack infiltrating immune cell phenotypes and functions, including highly plastic TAMs.[6-8] TAMs preferentially harness glycolysis for energy to contribute to the accumulation of lactate, enhance lipid intake and fatty acid oxidation (FAO) and upregulate Arg-1 and indoleamine 2,3-dioxygenase (IDO) expression, which results in the concentration changes of metabolites, such as ornithine and kynurenine, by affecting L-arginine and tryptophan metabolism. Concomitantly, TAMs also potentiate glutamate and glutamine metabolism. Metabolic reprogramming of glucose, lipid, and amino acid metabolism favors TAMs to maintain immunosuppressive phenotype and exert a pro-tumor function.

A series of metabolic reprogramming occurs in TAMs, and the efficacy of drugs targeting metabolic processes in reversing the immunosuppressive function of TAMs has been confirmed in mice and even in clinical studies. When metabolism targeted therapies are combined with immune checkpoint inhibitors (ICIs), efficacy is preferable, which provides more opportunities and options for future anti-tumor treatments. Nevertheless, the contradiction in metabolism between tumor cells and TAMs also presents challenges for clinical applications [Figure 1].

Glucose Metabolism

The "Warburg effect" occurs when tumor cells take up more glucose and make full use of aerobic glycolysis rather than OXPHOS to satisfy the demand for rapid

proliferation. Increased aerobic glycolysis in tumor cells leads to glucose starvation and lactate accumulation, resulting in an acidic and hypoxic TME.[8] Subsequently, TAMs undergo a sequence of changes in glucose metabolism in favor of an immunosuppressive function, which further induces TME remodeling. Upon depletion of glucose in the TME, tumor cells take up large amounts of glucose to satisfy growth requirements. Nevertheless, studies have elucidated that TAMs are the major consumers of glucose in the TME.[9] However, compared to TAMs, tumor cells are more dependent on glucose to support their growth.[10] Glucose competition induces metabolic reprogramming of glycolysis and OXPHOS in TAMs.

Glycolysis

Glycolysis is the process by which glucose is metabolized into pyruvate in the cytoplasm under anaerobic conditions. Thereafter, pyruvate is broken down into lactate under the catalysis of lactate dehydrogenase (LDH). The formation of dysfunctional tumor vasculature and the consumption of oxygen by tumor cells develop a hypoxic TME, which upregulates glucose transporter 1 (GLUT-1) expression and improves glucose uptake in TAMs, thus counteracting glucose consumption by tumor cells.[11-13] TAMs exhibit elevated glycolysis following increased glucose uptake. For instance, in an *in vitro* treatment of macrophages grown in human melanoma cell-conditioned medium, TAMs showed an elevated expression of the genes encoding GLUT-1 and hexokinase 2 (HK2).[14,15] In addition, proteomic analyses demonstrated that glycolysis related enzymes, involving HK2, were up-regulated in myeloid-differentiated macrophages induced by extracts from patients with breast cancer and in TAMs isolated from patients suffering from pancreatic cancer, portending an improved glycolytic availability in these cells.[16,17] This suggests that there is increased glucose uptake and specific expression of glycolysis key enzymes, leading to elevated glycolysis and lactate accumulation in TAMs. Previously, lactate was considered merely as a by-product of this metabolic process, but new evidence has revealed that it also has numerous prominent physiological effects, such as the promotion of the TCA cycle.[18,19] In our study, we found that lactate in malignant pleural effusions affected macrophages function by regulating the synthesis of norepinephrine. Lactate accumulation may alter the epigenetic landscape of TAMs, so they have the characteristics of M2-like macrophages.[20-22]

The hypoxic TME can induce the expression of hypoxia-inducible factor (HIF)-1α, a momentous transcriptional factor that regulates the transcription of many genes involved in the glycolytic pathway or glucose transport in TAMs.[11,23,24] Two major pathways are significantly potentiated by HIF-1α transcription: Toll-like receptor/nuclear factor-κB (NF-κB) and phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), which lead to an increase in glucose metabolism under oxygen-independent conditions.[25] Furthermore, HIF-1α promotes the transition of pyruvate to lactate via up-regulating the expression of these two enzymes: LDH (which catalyzes pyruvate to lactate) and pyruvate dehydrogenase kinase (which inactivates and restricts the entrance of pyruvate into the TCA cycle); further increasing lactate concentration.[13,25-27] Elevated lactate can motivate vascular endothelial growth factor (VEGF) expression and M2-like polarization of TAMs through HIF-1α mediation.[28] Taken together, enhanced glycolysis and elevated lactate concentrations produce immunosuppressive interactions in TAMs.

In the TME, tumor cells can also signal TAMs via lactate.[29] Lactate derived from tumor cells is transported into macrophages by monocarboxylic acid transporter (MCT) 1 and then generates pyruvate via LDH1, which has a competitive relationship with α-ketoglutarate (α-KG) to inhibit the expression of prolyl hydroxylase (PH), finally preventing proteasome degradation of HIF-1α, circumscribing ubiquitination, and triggering the glycolytic pathway.[30] Lactate derived from cancer cells potently induces Arg-1 in TAMs via stabilizing extracellular signal-regulated kinase 1/2 (ERK1/2), signal transducer and activator of transcription (STAT) 3 and HIF-1α, which stimulates tumor growth by suppressing T-cell responses.[15,28] With enhanced glycolysis in tumor cells and TAMs, the considerable glucose in the TME is reduced, which can lead to the suppression of T cell functions as well, thereby exacerbating the immunosuppressive capacity of the TME.[30-32] In the initial stages of tumorigenesis, TAMs preferentially utilize glycolysis for obtaining energy. However, with the accumulation of lactate in the TME and the gradual reduction of oxygen, OXPHOS predominates in later stages, meanwhile glucose uptake is reduced.[22,33,34]

Oxidative phosphorylation

TAMs can eventually differentiate into M2-like TAMs by increasing glycolysis and its metabolite lactate, culminating in exerting an immunosuppressive effect. Under these circumstances, tumor cells and infiltrating immune cells scramble the restrained glucose capacity. However, M2-like TAMs avoid this nutrient contention by preferentially utilizing OXPHOS.[35,36] OXPHOS is a common route that drives ATP synthesis by using the energy liberated during the decomposition of glucose, lipids, and amino acids. TAMs exhibit enhanced OXPHOS activity, thereby producing large amounts of ATP and completing the TCA cycle.[14,25] TAMs also exhibit high basal and maximal oxygen consumption rates and generate large quantities of mitochondrial ATP. In contrast, they have decreased PPP pathway expression, indicating that it may not be required for TAMs functions.[14,37] Despite increasing OXPHOS activity, TAMs express a glycolysis-dependent phenotype and are independent of OXPHOS and PPP.[37] Although glycolysis engenders less ATP per molecule of glucose than OXPHOS, it is fundamentally more significant for TAMs.

Lipid Metabolism

Lipids also ultimately generate ATP in the mitochondria via OXPHOS, which is critical for TAMs differentiation and function.[38] TAMs are loaded with a large quantity of lipid droplets, of which triglycerides (TGs), cholesterol, and phospholipids are the foremost components.[39-41]

TAMs enhance lipid metabolism to induce the $CD206^{+}$ major histocompatibility complex II^{low} immunosuppression phenotype.[42]

Fatty acid

Lipid deposition in TAMs leads to activation of genes associated with fatty acid β-oxidation, including carnitine palmitoyl transferase-1A (CPT1A) (an FAO rate-limiting enzyme).[15,38] The source of fatty acids is the breakdown of TGs, which are the predominant lipids.[43] TGs can be metabolized via adipose triglyceride lipase to diacylglycerols (DGs), which are decomposed by hormone-sensitive lipase (HSL) to monoacylglycerols (MGs) and by monoacylglycerol lipase (MAGL/MGLL) to free fatty acids and glycerol.[43,44] MGLL deficiency is a pivotal proportion leading to lipid accumulation in TAMs (the accumulation of MGs, DGs, and TGs); thus, macrophages activate an M2-like phenotype.[39,45] Consistent with this, lipid accumulation in TAMs was completely inhibited in a mouse model of MGLL overexpression.[46]

TAMs express high levels of the scavenger receptor CD36, accumulate lipids, and use FAO as energy source. TAMs ultimately lead to colorectal cancer progression since they are programmed to promote the ectopic activation of abhydrolase domain containing 5 (ABHD5), a well-documented activator of lipolysis without which TAMs may not survive due to a lack of FAO and energy production.[47] High FAO levels accelerate mitochondrial OXPHOS, generate reactive oxygen species (ROS), phosphorylate Janus kinase (JAK) 1 and dephosphorylate Src homology 2 domain-containing phosphatase-1 (SHP1), resulting in the activation and transcription of STAT6 to regulate TAMs generation and function, which are necessary to reeducate TAMs.[38]

Receptor interacting protein kinase 3 (RIPK3) deletion enhances FAO through the ROS/caspase 1/peroxisome proliferator-activated receptors (PPAR) pathway and promotes M2 polarization of TAMs, whose immunosuppressive function can be prominently reeducated through up-regulating RIPK3 or inhibiting FAO.[48] The activation of RIPK3 balances the storage and degradation of lipids in tumor cells in a time-dependent manner.[15] In addition, the breakdown of PPAR-γ depends on caspase-1, and disrupted PPAR-γ can translocate to the mitochondria, thereby negatively regulating FAO and inducing lipid droplet accumulation and TAMs differentiation.[15,49] In our research, we found that, after interacting with tumor cells, TAMs regulated the expression of chemokine (C-C motif) ligand 20 (CCL20) through the lipid metabolism pathway; consequently, TAMs can exert their immunosuppressive effect. In summary, FAO is critical for TAMs survival and immunosuppressive phenotypes. Inhibition of fatty acid metabolism in TAMs has been proposed as a strategy to strengthen anti-tumor effects.[50]

Cholesterol

TAMs can utilize scavenger receptors including CD36 to take up lipids, which are decomposed into free cholesterol and fatty acids by lysosomal acid lipases in the lysosomes.[51] Solid neoplasms show high levels of free cholesterol and cholesteryl esters, although these are relatively absent in TAMs.[52] In our study, we observed that, in TAMs, increased cholesterol efflux led to a decrease in intracellular cholesterol content and inflammatory factors, resulting in immunosuppression. In addition, ovarian tumor cells promote the efflux of membrane cholesterols, which causes the formation of the M2-like TAMs and stimulates tumor progression.[53] This may be one of the reasons for the reduction in intracellular cholesterol levels in TAMs.

The cholesterol transporters ATP-binding cassette transporter A1/G1 (ABCA1/G1) mediate the reversal of cholesterol transport in macrophages.[54] The outward migration of TAMs membrane cholesterol enhances the IL-4 signaling pathway and inhibits interferon (IFN)-γ-induced gene expression, leading to pro-tumor effects.[55] The loss of intracellular cholesterol supports the conversion of macrophages into M2-like TAMs; thus, cholesterol transporters play a vital role in macrophage polarization.[56] Therefore, elevated cholesterol efflux is beneficial for maintaining the immunosuppressive phenotype of TAMs.

Phospholipids

Phosphatidylcholine and phosphatidylglycerol, the main cell surfactant components, are present at low levels in tumor tissues.[52] Phospholipids are the source of lipid second messengers that activate the PI3K/AKT/mTOR pathway, which is relevant to tumorigenesis and cancer progression and causes poor prognosis.[57] Arachidonic acid (AA), a widely studied phospholipid subgroup, is integral to the regulation of inflammation and cancer.[39] Free AA can be transformed into prostaglandins, oxygenated fatty acids, and leukotrienes via three major pathways, one of which is the cyclooxygenase (COX) pathway.[58] Phospholipid metabolism changes in TAMs after infiltration of the TME since COX1/2 are generally altered in diverse phases of macrophages development.[59] Prostaglandin E2 (PGE2) is a metabolite produced by AA under the mediation of COX2, which can be secreted into the TME to stimulate TAMs to produce chemokines beneficial to tumors, for which TAMs express a pro-tumor phenotype.[60,61]

Amino Acid Metabolism

In addition to the remodeling of glucose and lipid metabolism mentioned above, a large number of recent studies have revealed the reprogramming of amino acid metabolism in TAMs. TAMs upregulate the expression of Arg-1 and IDO and enhance glutamine synthesis and catabolism, which in turn leads to the accumulation of the corresponding metabolites. These changes favor polarization of TAMs into M2-like TAMs [Figure 2].

Arginine metabolism

As previously mentioned, TAMs maintain an immunosuppressive phenotype via upregulating the expression of

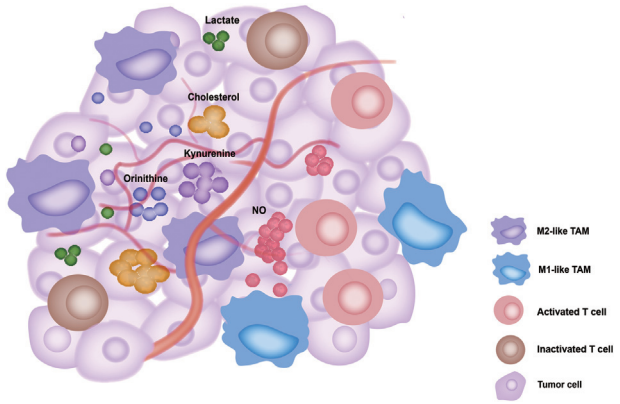

Figure 2: M2-like TAMs undergo metabolic reprogramming, leading to changes in a series of metabolites in the TME to inhibit T cell activation. The accumulation of lactate (a metabolite from the anaerobic metabolism of glucose), kynurenine (a metabolite from tryptophan metabolism), and ornithine (a metabolite from arginine metabolism), and the efflux of cholesterol from TAMs inhibit infiltrating T cell functions at different degrees, further enhancing the immunosuppressive function of TME. In contrast, M1-like TAMs exert opposite functions, such as increasing NO production to inhibit tumor progression. NO: Nitric oxide; TAM: Tumor-associated macrophage; TME: Tumor microenvironment.

Arg-1, resulting in a decrease in L-arginine and changes in the corresponding metabolites. The catabolism of L-arginine is mediated by Arg-1 and iNOS, which compete for the substrate L-arginine, generating a variety of metabolites that play diverse roles in tumors. It has been reported that TAMs can activate the transcription of Arg-1, which stimulates the breakdown of L-arginine into ornithine and urea. Interestingly, high levels of L-arginine in cells are essential for T cells survival and proliferation.[62,63] Depletion of L-arginine due to Arg-1 activation in TAMs promotes adjacent tumor cells and cause cancer progression.[64] Therefore, Arg-1 activity in TAMs can induce a pro-tumor phenotype, reducing T cells proliferation and cytokine production, which results in immunosuppression in the TME.[65] TAMs-derived ornithine favors the proliferation of tumor cells and can be converted by ornithine decarboxylase (ODC) into polyamines, including putrescine, spermidine, and spermine, thereby stimulating M2-related gene expression and stabilizing the tumor-promoting phenotype of TAMs.[66-69] Furthermore, ODC constrains M1-like TAMs activation through chromatin modification, leading to immunosuppression of TME.[67] TAMs preferentially take advantage of the Arg-1 pathway to metabolize L-arginine and form a competitive relationship with the iNOS pathway, which results in a deficit of NO.[70,71] Besides, NO can prevent M1-like phenotype to M2-like repolarization, because the inhibition of iNOS enables M1-like TAMs to repolarize into the M2-like phenotype upon exposure to IL-4 after LPS plus IFN-γ treatment. In the TME, a decline in NO levels increases the M2 phenotype and leads to immunosuppression.[72] Both the Arg-1 and iNOS pathways have been observed in TAMs, representing the M1/M2 phase in the ischemic tumor domain.[25] Co-expression of Arg-1 and iNOS at low arginine concentrations may be beneficial for the generation of ROS and reactive nitrogen species, and then suppresses the function of T cells in tumors. The remodeling of L-arginine metabolism in TAMs apparently favors the immunosuppressive phenotype.

Tryptophan metabolism

In malignant tumors, TAMs can deplete tryptophan in the local microenvironment through its uptake and catabolism, ultimately leading to immunosuppression.[73,74] Both TAMs and tumor cells can activate IDO to remodel the immunosuppressive environment through tryptophan consumption and the accumulation of tryptophan metabolites (kynurenine, 3-hydroxyanthranilate, and quinoline).[75,76] TAMs may strongly express IDO, which catabolizes tryptophan to kynurenine, an endogenous aryl hydrocarbon receptor (AHR) ligand.[77,78] Moreover, kynurenine can potently suppress the immune response of T cells; by mimicking AHR, kynurenine skews the conversion of naive T cell toward fork headbox p3 $(FOXP3)^+$ regulatory T cell (Treg) and suppresses Th17 cell differentiation.[77,79] IDO^+ TAMs inhibit T-cell viability, whereas pre-treatment of TAMs with IDO inhibitors reserves T-cell proliferation.[15,78,80] IDO activation can be induced by tumor necrosis factor-α, IFN-γ or prostaglandins, but TAMs squint toward the M2-like phenotype if IDO is over-expressed, while IDO silencing triggers an anti-tumor macrophage profile.[81] Therefore, TAMs can increase kynurenine by up-regulating IDO to consume tryptophan, which can produce immunosuppressive effects in the TME.

Glutamine and glutamate metabolism

The effects of glutamate metabolism in TAMs on their functional phenotypes have rarely been investigated.[5] In the TME, glutamine and glutamate have the same function; they provide energy to TAMs. In addition, glutamine powers tumor cells by being released into the TME.[69,82] Glutamatergic regulation of macrophages may be involved in the polarization of macrophages toward an immunosuppressive phenotype.[83] Moreover, glutamine deprivation has a substantial effect on M2 polarization.[84] Targeting glutamine metabolism promotes reprogramming and the pro-inflammatory phenotype of TAMs.[85] Glutamine synthetase (GS), an enzyme that synthesizes glutamine from glutamate, is probably maintaining the phenotype of M2-like TAMs. Inhibition of GS can reverse M2-like macrophages to an M1-like phenotype, manifested by lessened intracellular glutamine and incremental succinate.[86,87] TAMs in Lewis lung carcinoma (LLC) mouse models and patients with glioblastoma have been found to upregulate GS, which is induced in response to starvation and can elicit pro-tumorigenic TAMs polarization.[29,82] Macrophage-specific knockdown of GS reverses LLC-associated TAMs polarization to an anti-tumor phenotype and attenuates metastasis.[87] Not only is GS-mediated phenotypic transformation of macrophages significant, but glutamine catabolism also plays an essential role. It has been reported that α-KG from glutamine catabolism is critical for the alternative activation of macrophages (M2). Succinate is synthesized by c-aminobutyric acid and possibly promotes a partial reversal of the M2 phenotype to an M1-like phenotype.[28,88] A high α-KG/succinate proportion modulates M2 promotion, whereas a low proportion strengthens the pro-inflammatory phenotype of classically activated (M1) macrophages.[88] In summary, an increase in glutamine anabolism and

catabolism is beneficial for inducing the transformation of TAMs to an M2-like phenotype.

Others

Iron metabolism

Iron is a potential mutagen that can cause tumor cells to behave more aggressively.[89,90] Tumor cells require excess iron at all times, and TAMs are key sources of iron. TAMs release iron into the TME to increase its availability.[91] Iron also influences the polarization of TAMs. Moreover, heme oxygenase 1-mediated activation of iron metabolism also contributes to TAMs polarization.[92] Intracellular iron deficiency may result in HIF activation, whereas high intracellular iron concentrations may induce an M1-like phenotype.[93,94] Hence, M2-polarized macrophages are set in an iron-export mode, while M1-polarized macrophages in an iron-retention mode.[95,96]

Nucleotide metabolism

Extracellular adenosine is a tumor metabolite that makes an impact on TAMs functions, phagocytosis and cytokine production. Adenosinergic signaling mediates various suppressive functions in infiltrating immune cells.[97,98] Myeloid cells devoid of adenosine receptor A2A prevent tumor progression and metastasis in a malignancy model.[99] In our study, A2A upregulated macrophages secretion of chemokine (C-X-C motif) ligand 5 (CXCL5) via the NF-κB pathway.

Reversing the Immunosuppression of TAMs Through Targeting Metabolism-Related Pathways

Due to TME remodeling, TAMs ultimately retain an immunosuppressive phenotype by reprogramming glucose, lipid, and amino acid metabolism. Targeting the metabolism-related pathways of TAMs presumably is conducive to the production of M1-like TAMs and thereby alters their immunosuppressive function. Simultaneously, the metabolism of tumor cells undergoes corresponding changes. Therefore, further studies are needed to determine whether treatments targeting metabolism-related pathways have anti-tumor effects.[100] Nonetheless, targeting metabolism-related pathways has been shown to be effective in suppressing tumors in mice and even in clinical trials, which works better in combination with ICIs, even in refractory tumors.[101,102]

Targeting glucose metabolism

At present, targeting the glucose metabolism-related pathways of TAMs is mainly focused on diminishing glycolysis to regulate the immunosuppressive effect of TAMs. 2-deoxyglucose (2-DG) can block the glycolytic pathway, thereby disrupting the polarization of M2-like TAMs. In addition to decreasing glycolysis, 2-DG impairs OXPHOS, resulting in the inhibition of ATP production, activation of JAK-STAT6, and failure of M2 polarization.[103,104] Meanwhile, in multiple *in vitro* and *in vivo* studies, 2-DG inhibited cancer cells survival, proliferation, and motility when combined with other targeted therapies; 2-DG has been used in clinical trials for tumor therapies, but it has exhibited strong toxicity.[105,106]

Although 2-DG has demonstrated toxicity in clinical trials, extensive malignancies have been treated with mTOR inhibitors, which can also inhibit glycolysis. In multiple mouse tumor models, it has been shown that hypoxia promotes the expression of DNA damage-inducible transcript 4 (DDT4, especially regulated in development and DNA damage response 1 [REDD1]), a well-known endogenous blocker of the mTOR complex 1 (mTORC1) in TAMs.[22] Thus, TAMs preferentially utilize oxidative metabolism while reducing glucose uptake under hypoxic conditions,[22] which has relationship with an enhanced angiogenic reaction and the formation of abnormal leaky blood vessels. It has been proved that mTORC1 inhibitors are paradoxically beneficial for tumor development due to glycolytic inhibition combined with activation of the neovascularization program.[22] Blockade of VEGFA expression in TAMs not only inhibits glycolysis, but also is detrimental to neo-angiogenesis, thereby reducing the infiltration of TAMs in the TME.[107,108]

Remarkably, therapeutic suppression of LDHs and/or MCTs predisposes TAMs toward an anti-tumor function and damages angiogenesis in malignancies. Several LDH and MCT inhibitors have entered phase I/II clinical trials, including AT-101 (a non-specific LDH inhibitor) and AZD3965 which can inhibit MCT1/2 expression.[109,110]

Besides, some drugs commonly used in the clinical treatment of non-tumor diseases have been shown to improve the inhibitory function by affecting the glucose metabolism of TAMs. Preclinical studies have demonstrated that the respiratory complex I inhibitor, metformin, can affect TAMs polarization by inhibiting M2-like reprogramming.[111-113] Acyclovir is an antibacterial and antiviral drug that polarizes macrophages to an M1-like anti-tumor phenotype by blocking the HIF-1 pathway and enhancing glucose uptake by pancreatic ductal adenocarcinoma.[114] These phenomena delineate that targeting the glucose metabolism pathway in TAMs is a promising direction.

Targeting lipid metabolism

The efficacy of targeting lipid metabolism has also been demonstrated in various mouse tumor models. Etomoxir is widely used as a CPT1 specific inhibitor.[115] CPT1 is upregulated by fatty acid uptake and oxidation.[46] Studies have indicated that etomoxir can inhibit the M2-like phenotype of TAMs and their precursor activity.[116]

Simvastatin can disrupt lipid rafts and is generally employed to decrease cholesterol level in clinical practice, which repolarizes TAMs and promotes the conversion of M2-like TAMs to the M1-like phenotype through cholesterol-related liver X receptor/ABCA1 modulation.[117] In addition, TAMs from mouse breast cancer models, especially M1-like phenotype, enhanced the expression of epithelial

fatty acid binding protein (E-FABP), an intracellular lipid chaperone. Stimulation of TAMs with an E-FABP activator (EI-05) can significantly inhibit tumor growth by increasing lipid drop formation and IFN-β production.[118]

Targeting amino acid metabolism

Targeting pathways related to amino acid metabolism has shown remarkable efficacy. JHU083 is a precursor drug that extensively inhibits glutamine metabolism enzymes, targets glutamine metabolism, and reconstructs TAMs into an M1-like phenotype, strengthening anti-tumor therapies without influencing the total TAMs in tumors.[85] JHU083 also blocked glutamine metabolism in tumor cells, thereby inhibiting tumor growth in various mouse tumor models.[119]

TAMs up-regulate Arg-1 expression through the PI3K/AKT/mTOR pathway, resulting in an enhancement of the L-arginine metabolism, leading to immunosuppression. In mouse experiments, deletion of PI3Kγ and PIK3cg can inhibit the expression of Arg-1 and increase iNOS correspondingly, leading to an increase in intracellular L-arginine content, which ultimately results in immune activation and tumor suppression.[120,121]

Except for arginine metabolism, we have described above that TAMs strongly express IDO, thereby decomposing tryptophan and eventually producing inhibitory effects on T cells, resulting in an immunosuppressive function. For example, high IDO1 expression in sentinel lymph nodes was intimately related to tumor infiltrating lymphocyte reduction and poor prognosis in patients with melanoma.[122] Immunotherapy-treated IDO-knockout melanoma mice were found to live longer. IDO-inhibiting drugs hold promise as a new strategy for adjuvant therapy in IDO-expressing cancers [Table 1].[123,124]

Synergistic Application of Metabolism-Targeted Therapy and ICIs

Studies have found that the signaling level of programmed cell death ligand 1 (PD-L1) on TAMs affects the disease progression of melanoma and ovarian cancer, and that blockage of programmed cell death 1 (PD-1) and PD-L1 expression in TAMs can partially restore M1-like phenotype and function,[125,126] suggesting that combination of metabolism-related therapy and ICIs may address some bottlenecks in immunotherapy.

TAMs over-express COX2 and microsomal prostaglandin E synthase 1 (mPGES1), which promotes AA to activate PGE2, directly associated with PD-L1 expression.[127] Combination therapy with celecoxib (a selective COX2 inhibitor which boosts tumor cells apoptosis) and anti-PD-1 inhibits PD-L1 expression in B16-F10 melanoma and 4T1 breast cancer models.[128,129] Studies have found that 2,4-dinitrophenol (DNP) simultaneously restrained the expression of COX2 and PD-L1, inhibited the secretion of prostaglandins, blocked the oncogene c-Myc, and depressed the breast cancer (BC)-related protein bromodomain-containing protein 4 production and ERK1/2 phosphorylation in BC cells. DNP also exhibited strong anti-tumor effects in a triple-negative breast cancer (TNBC) mouse model.[130]

The co-expression of PD-L1 and lactate dehydrogenase A (LDHA), which are exceedingly expressed in TNBC cells and tissues, is related to adverse outcomes in TNBC. Both PD-L1 and LDHA functions are inhibited by miR-34a. Combining immunotherapy and metabolic therapy targeting PD-L1 and LDHA might be beneficial for the treatment of breast cancer (especially TNBC).[131] High levels of IDO1 exert an immunosuppressive effect, inhibiting the efficacy of anti-cytotoxic T lymphocyte associated antigen 4 and (PD1/L1) treatments, whereas the response to immunotherapy and chemotherapy is enhanced when IDO1 expression is suppressed.[132,133] A phase I/II clinical research indicated that the combination of nivolumab and IO102/IO103, an investigational vaccine targeting IDO and PD-L1, decreased tumor burden and increased progression-free survival.[134]

Conclusions and Perspectives

Reprogramming of cellular energy metabolism is an emerging hallmark of cancer.[135] In this review, we expound the metabolic reprogramming of TAMs connected with their immunosuppressive function. We elaborate on the glucose, lipid, and amino acid metabolism modifications needed for TAMs reprogramming. TAMs increase glycolysis and FAO, promote cholesterol efflux, up-regulate Arg-1 and IDO expression to elevate arginine and tryptophan metabolism, and enhance glutamine and glutamate metabolism, which ultimately favor TAMs to maintain an immunosuppressive phenotype.

Based on these metabolic changes, therapies targeting metabolism-related pathways have also been found to have favorable effects. In combination with PD-1/L1, inhibitors of COX2 and LDHA have also achieved encouraging results in refractory tumor models. Although immune checkpoint therapy has shown surprising efficacy, strategies targeting TAMs have gradually attracted attention in order to further address the tolerance phenomenon that occurs during treatment, but almost all of them are in the preclinical stage. Targeting TAMs reprogramming has shown potential for the therapeutic strategies of solid tumors.[136,137] This suggests that targeting metabolism-related pathways may provide new opportunities and options for future tumor immunotherapy. However, many questions remain unanswered: As the TME is a metabolically interrelated whole, how does targeting metabolism affect other immune cells? What about the serious adverse reactions associated with targeted metabolism, such as those associated with 2-DG? How can the TME metabolism balance be restored? With the continuous in-depth study of TAMs-related metabolism in the TME, we will open a new chapter in anti-tumor therapy.

Table 1: Summary of clinical trials targeting metabolism-related pathway.

Targeted metabolism	Molecular target	Agent	Metabolic changes	Effects on TAMs	Identifier	Stage	Conditions
Glucose metabolism	BRAF	Phenformin	Upregulates GLUT-1 or GLUT-3; inhibits OXPHOS	Reduces polarization and infiltration of M2-like TAMs	NCT03026517	I	Melanoma
	Hexokinase 2	2-deoxyglucose (2-DG)	Inhibits glucose uptake and glycolysis	Converts M2-like TAMs to M1-like TAMs	Completed (stopped due to toxicity)	I	Cancer in general
	HIF-1α	EZN-2968	Inhibits HIF-1α	None	NCT01120288	I	Advanced solid tumors with liver metastasis
Lipid metabolism	COX1/2	Aspirin	Suppresses oxidative stress and ROS metabolism	Increases M1 marker expression while decreases that of M2	NCT04188119 NCT02659384	II	Ovarian cancer, HNSCC, TNBC, solid adult tumor, multiple myeloma
	HMGCR	Lipophilic statins (simvastatin and lovastatin)	Influences cholesterol metabolism and reduces lactate production	None	NCT03275376 NCT03324425	II	Hepatocellular carcinoma, squamous cell carcinoma, NSCLC, breast cancer
	SREBP-2	Fatostatin	Inhibits the production of fatty acids and cholesterol synthesis; causes mitotic arrest	None	None	None	Prostate, pancreatic, and endometrial cancers
Amino acid metabolism	mTOR	Ridaforolimus	Influences amino acid, glucose, nucleotide, fatty acid, and lipid metabolisms	Promotes M2 differentiation to cytotoxic M1 phenotype	NCT00086125 NCT00122343 NCT00538239	III/Done	Hematological malignancies, metastatic endometrial cancer, sarcoma
	IDO1	Epacadostat	Inhibits tryptophan metabolism; reduces kynurenine	Reeducates M2-like TAMs to M1-like	NCT03832673	II	Muscle-invasive urothelial cancer of the bladder
	Arginase-1	L-norvaline and CB-1158	Increases arginine metabolism via iNOS, increasing NO	Reeducates M2-like TAMs to M1-like	NCT02903914 NCT03314935	I/II	Advanced solid tumors
	GLS	CB-839	Inhibits glutamine metabolism	Activates proinflammatory TAMs	NCT03875313 NCT02861300	I/II	Colorectal cancer, NSCLC, renal cell carcinoma, melanoma
Adenosine metabolism	CD73	Oleclumab	Reduces adenosine production	Enhances M1 macrophages predominance	NCT04262375	II	Renal, pancreatic, head and neck cancer, and NSCLC with DNA methylation
Nucleotide biosynthesis	DHFR GARFT	Methotrexate Pemetrexed	Impairs nucleotide biosynthesis	None	NCT00808639	II	Breast cancer

COX1/2: Cyclooxygenase 1/2; DHFR: Dihydrofolate reductase; GARFT: Glycinamide ribonucleotide formyltransferase; GLS: Glutaminase; GLUT: Glucose transporter; HIF-1α: Hypoxia-inducible factor-1α; HMGCR: 3-hydroxy-3-methyl glutaryl-coenzyme A reductase; HNSCC: Head and neck squamous cell carcinoma; IDO1: Indoleamine 2,3-dioxygenase 1; iNOS: Inducible nitric oxide synthase; mTOR: Mammalian target of rapamycin; NO: Nitric oxide; NSCLC: Non-small cell lung cancer; OXPHOS: Oxidative phosphorylation; ROS: Reactive oxygen species; SREBP-2: Sterol regulatory binding protein-2; TAMs: Tumor-associated macrophages; TNBC: Triple negative breast cancer.

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Conflicts of interest

None.

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