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REVIEW

Immunometabolism: a new dimension in immunotherapy resistance

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Abstract Immune checkpoint inhibitors (ICIs) have demonstrated unparalleled clinical responses and revolutionized the paradigm of tumor treatment, while substantial patients remain unresponsive or develop resistance to ICIs as a single agent, which is traceable to cellular metabolic dysfunction. Although dysregulated metabolism has long been adjudged as a hallmark of tumor, it is now increasingly accepted that metabolic reprogramming is not exclusive to tumor cells but is also characteristic of immunocytes. Correspondingly, people used to pay more attention to the effect of tumor cell metabolism on immunocytes, but in practice immunocytes interact intimately with their own metabolic function in a way that has never been realized before during their activation and differentiation, which opens up a whole new frontier called immunometabolism. The metabolic intervention for tumor-infiltrating immunocytes could offer fresh opportunities to break the resistance and ameliorate existing ICI immunotherapy, whose crux might be to ascertain synergistic combinations of metabolic intervention with ICIs to reap synergic benefits and facilitate an adjusted anti-tumor immune response. Herein, we elaborate potential mechanisms underlying immunotherapy resistance from a novel dimension of metabolic reprogramming in diverse tumor-infiltrating immunocytes, and related metabolic intervention in the hope of offering a reference for targeting metabolic vulnerabilities to circumvent immunotherapeutic resistance.

Keywords immune cell; immunometabolism; metabolic reprogramming; immunotherapy; resistance; tumor microenvironment; immune checkpoint inhibitor

Introduction

Immune checkpoint inhibitors (ICIs) targeting immune checkpoint proteins, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1), have demonstrated unparalleled and impressive clinical responses in various tumor types and considerably revolutionized the paradigm of tumor treatment [1]. Whereas 60% to 80% of patients remain unresponsive or develop resistance to ICIs as a single agent, which remains a momentous limitation, particularly in the treatment of solid tumors [2–4]. When coupled with the apparent toxicity and high cost of ICIs, hunting for ideal approaches to boosting response rate and duration to these immunotherapies is a pivotal issue that must be urgently addressed.

The scarcity of response to ICI therapy may be the consequence of cellular metabolic dysfunction in that a mounting number of studies have shed light on the indispensable role that cancer-induced metabolic reprogramming plays in the development of ICI resistance [5–7]. Although dysregulated metabolism (e.g., aerobic glycolysis also known as the Warburg effect) has long been adjudged as a hallmark of tumor, it is now increasingly accepted that metabolic reprogramming is not exclusive to tumor cells, but is also characteristic of

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immune cells [8–12]. On account of over-exploitation of nutrients such as glucose, amino acids and fatty acids (FAs) through competition by rapidly proliferating tumor cells that possess substantial requirements of biosynthesis, the nutrients vital for functions of immune cells infiltrating the tumor microenvironment (TME) are depleted, which not only ensues a nutrient-deficient TME for immune cells [5,13–15], but also accelerates the generation of dynamic and deleterious metabolic waste in tumor cells, such as lactate and methylglyoxal by-products that can further foster an immunosuppressive TME [8,14–16]. Such an inhospitable environment forces immune cells to undergo metabolic reprogramming to survive so that the immunosuppression function of suppressor cells or tumor-promoting cells is elevated whereas anti-tumor immune cells differentiate or polarize into immunosuppressive phenotypes and even are deprived of anti-tumor functions during the process, thereby ultimately constructing a potently immunosuppressive TME that abrogates immunosurveillance and foments tumor immune evasion and metastasis [5,8,12–14]. Therefore, the highly dysregulated metabolism in immune cells infiltrating the TME is bound to make remarkable impacts on the efficacy of anti-cancer ICI immunotherapy.

Altogether, people used to pay more attention to the effect of tumor cell metabolism on immunocytes, but in practice the immunity of immunocytes interact intimately with their own metabolic function in a way that has never been realized before during their activation and differentiation, which opens up a whole new frontier called immunometabolism [11,12,17–21]. There is support for the notion that metabolic transition of immune cells infiltrating the TME transforms the phenotype and function of themselves, which is recognized to at least partially conduce to the failure of current tumor immunotherapy. Hence, the metabolic intervention for immune cells infiltrating the TME could offer fresh promising opportunities to break the resistance and ameliorate existing ICI immunotherapy, and notably, its crux might be to ascertain synergistic combinations of metabolic intervention with ICIs to reap synergic benefits and facilitate an adjusted anti-tumor immune response [6,22–24].

Consequently, this review attempts to expound potential mechanisms underlying ICI resistance from a novel perspective of metabolic reprogramming in diverse immune cells infiltrating the TME. Furthermore, we elaborate recent advances in studies of metabolic intervention on the basis of metabolic reprogramming in immune cells in the hope of offering a reference for targeting metabolic vulnerabilities to circumvent immunotherapeutic resistance. Herein, we will in detail dissect the above gist chiefly from metabolic reprogramming of three major nutrient substance in the following five types of intratumoral immune cells: T cell, natural killer (NK) cell, dendritic cell (DC), macrophage, and myeloid-derived suppressor cell (MDSC).

Overview of immune cell metabolism

There are many diverse immune cells in the immune system, including T cell, NK cell, DC, macrophage, neutrophil, monocyte, eosinophil, basophil. When the body is in a stable state, these cells are in the resting state. However, when the body is triggered by infection, inflammatory cytokines, or other external agents, these cells are immediately activated, differentiate and react. There are dramatic differences both in energy utilization and effector function in resting and active immune cells where they will manifest completely divergent metabolic patterns according to differentiation of diverse cell subsets (Fig. 1).

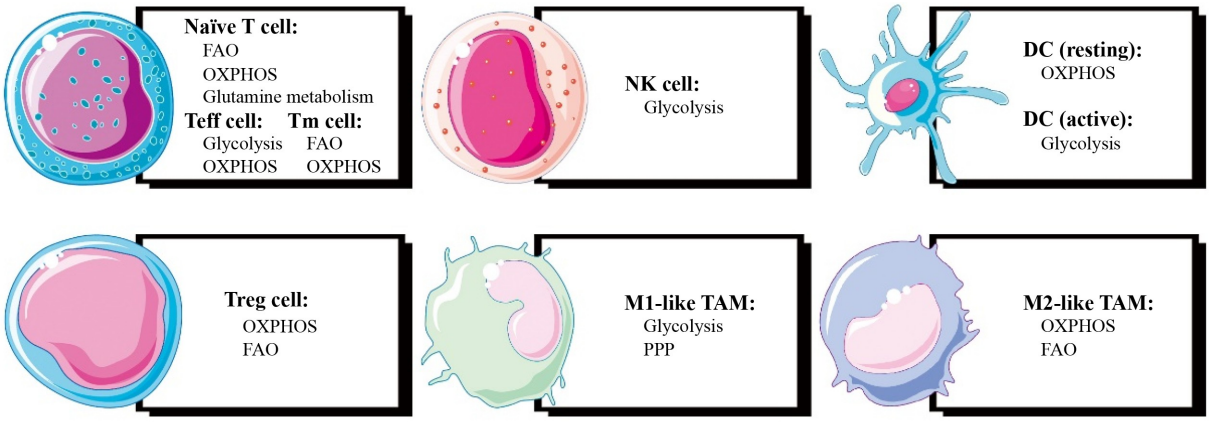

Fig. 1 Overview of immune cell metabolism. Each type of immune cell and their resting or active state manifest completely divergent metabolic patterns. Abbreviation: Teff cell, effector T cell; Tm cell, memory T cell; Treg cell, regulatory T cell; NK cell, natural killer cell; DC, dendritic cell; TAM, tumor-associated macrophage; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway.

Metabolic reprogramming of immunocyte and related metabolic interventions

Glucose metabolic reprogramming and related metabolic interventions of immune cells

T cells

The metabolic properties of glucose are diverse in distinct subsets of T cells (Fig. 1) [25,26]. Naïve T cells circulate throughout the body hunting for antigen, requiring tiny amounts of glucose to generate adenosine triphosphate (ATP) through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) so as to sustain their actions [25]. Mammalian target of rapamycin (mTOR) has a pivotal role in modulating quiescent and active state of naïve T cells [27]. mTOR has two different structures and functions: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 induces Myc transcription, while mTORC2 overexpresses glucose transporter 1 (GLUT1) and thereby enlarges glucose ingestion [27]. During the activation of naïve T cells to activated T cells, there is a metabolic shift from OXPHOS to aerobic glycolysis upon T cell receptor (TCR) engagement and co-stimulation, thereby generating ATP faster and driving macromolecule biosynthesis [25,27]. Because glucose is the sole energy source for effector T cells (Teff cells), both $CD4^+$ T helper cells (Th cells) and $CD8^+$ cytotoxic T lymphocytes (CTLs) express GLUT1, rely on glycolysis to execute their function, and depend on mTOR signaling to maintain their glycolytic activity [6].

Unfortunately, the deviant bioenergetic activity that allows tumor cells to rapidly consume a great deal of glucose through glycolysis even in the presence of sufficient oxygen is a phenomenon known as the Warburg effect, which possesses a ten times efficiency of activated T cell ingestion of glucose so severely impairs the cytolytic activity and the generation of antineoplastic effector molecules of Teff cells in a manner linked to restriction in the glucose bioavailability, mTOR activity, nuclear factor of activated T cell (NFAT) signaling and glycolytic capability in tumor-infiltrating Teff cells (Fig. 2) (Table 1) [28,29]. For instance, $CD8^+$ T cells express the low-level vital tumoricidal effector molecules perforin and granzymes B and C (Gzms-B/C) in the context of glucose-deprivation [30]. Intriguingly, autophagic activity is raised to sustain survival under the stress of nutrient depletion [31], but autophagy associated gene ATG5 represses GLUT1 expression, thereby impeding glycometabolism, the transition to an effector memory phenotype, and the generation of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) in $CD8^+$ T cells [32]. Thus, insufficient glycolysis leads to decreased activity of $CD8^+$ T cells and anti-tumor dysfunction [33], and glucose limitation within the TME also triggers T cell anergy or even apoptosis via the Noxa/Mcl-1 axis [34]. Fortunately, triggering lipid kinase acylglycerol kinase (AGK) can promote the glycolysis and functional fitness of $CD8^+$ T cells via inactivating PTEN and boosting mTOR activity, thereby improving anti-tumorigenic activity [35]. Analogously, although T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) mediates $CD3^+$ T cell glycolytic dysfunction and accelerates the proliferation and immune evasion of tumor cells in colorectal cancer, co-blockers of TIGIT and PD-1 synergistically reverses the suppressed glucose metabolic activity of T cells and presents an efficacious suppressing effect on tumor progression in a human colorectal xenograft mice model [36]. Notably, blockading tumor cell glycolysis and improving glucose availability within the TME can also preserve antineoplastic T cell immunity and promote response to ICIs [37]. The dimethyl fumarate, for instance, can repress aerobic glycolysis of tumor cells and normalize metabolic competition between tumors and T cells, which potentiates anti-tumor immunity of tumor-infiltrating $CD8^+$ T cells, thereby optimizing the efficacy of ICIs and interleukin-2 (IL-2) therapy while eliminating severe toxicity induced by IL-2 immunotherapy [38]. Additionally, compared to either metformin or anti-PD-1 antibody alone, the administration of metformin with anti-PD-1 antibody intensifies the capability of $CD8^+$ T cells to release effector cytokines [39]. Therefore, as a widely prescribed drug for type II diabetes, metformin also has a synergistic effect with ICIs on stimulating T cell functions and eradicating tumor cells. Metformin combined with ICIs are now being tested in several clinical trials to investigate if the combination can produce better clinical results than monotherapy (ClinicalTrials.gov ID: NCT04414540, NCT03048500, NCT03618654 and NCT03311308). For another, bountiful tumor-derived lactate resulted from efficient aerobic glycolysis can debilitate anti-tumor immune responses via varying pyruvate utilization and then intercepting succinate signaling in $CD8^+$ T cells, but the blockade of pyruvate dehydrogenase is sufficient to rehabilitate cytotoxicity of $CD8^+$ T cells via recovering pyruvate carboxylase activity, succinate secretion, and the activation of succinate receptor [40]. Meanwhile, as a glycolytic metabolite of $CD8^+$ T cells and $CD4^+$ T cells, discounted generation of phosphoenolpyruvate (PEP) mediated by the competition for glucose by tumor cells is inimical to T cell immunosurveillance, which could be associated with the flawed Ca^{2+}-NFAT signaling and T lymphocyte activation [28]. To this end, transferring genetically engineered tumor-specific $CD8^+$ T cells and $CD4^+$ T cells

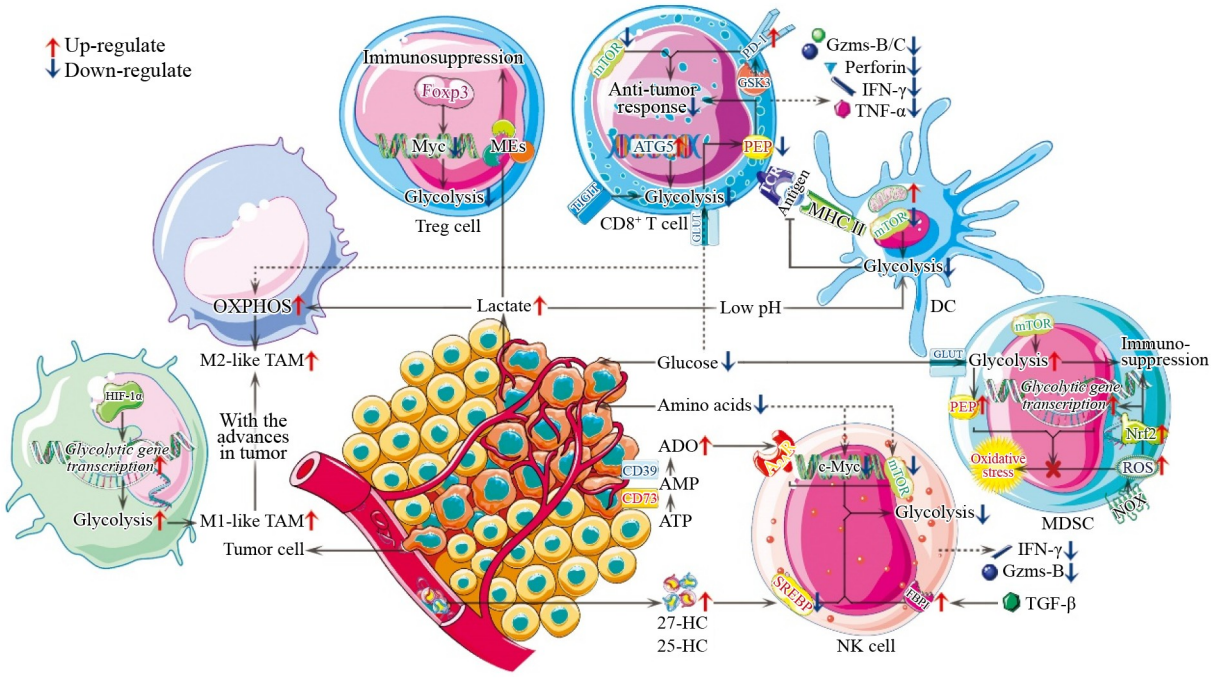

Fig. 2 Resistant mechanism of immunotherapy: glucose metabolic reprogramming of immune cells within the TME. In the TME, tumor cells interfere with immune cell function by forcing immune cells to reprogram glucose metabolism. Specifically, metabolically highly active tumor cells deplete large amounts of nutrients (e.g., glucose and amino acids), which represses glycolysis of $CD8^+$ T cells, NK cells, and TAMs by limiting the availability of glucose to $CD8^+$ T cells and TAMs and amino acids to NK cells, and generate immunosuppressive metabolites (e.g., lactate, ADO), which attenuates glycolysis of DCs while accentuating mitochondrial respiration by acidifying the TME, sustains immunosuppressive identity of Treg cell by exploiting lactate by various metabolic enzymes, skews M1-like toward the polarization of M2-like TAMs by underscoring OXPHOS, and inhibits OXPHOS and glycolysis of NK cells by activating $A_{2A}R$ by ADO. When MDSCs are confronted with tumor-derived factors, they upregulate glycolytic genes and thereby ingest glucose as the greatest capability as possible. The glucose metabolic reprogramming ultimately emasculates the effector function of $CD8^+$ T cells, DCs, NK cells, M1-TAMs, while invigorating the immunosuppressive function of Treg cells, M2-TAMs, and MDSCs, which contributes to immunotherapy resistance. Abbreviations: TME, tumor microenvironment; PD-1, programmed cell death-1; Gzms-B/C, granzymes B and C; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor β; GSK3, glycogen synthase kinase 3; mTOR, mammalian target of rapamycin; PEP, phosphoenolpyruvate; MEs, metabolic enzymes; TCR, T cell receptor; TAM, tumor-associated macrophage; Treg cell, regulatory T cell; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; NK cell, natural killer cell; ROS, reactive oxygen species; GLUT, glucose transporter; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; SREBP, sterol regulatory element binding protein; ATP, adenosine triphosphate; AMP, adenosine 3′-monophosphate; ADO, adenosine; $A_{2A}R$, A_{2A} receptor; 25-HC, 25-hydroxycholesterol; 27-HC, 27-hydroxycholesterol; HIF-1α, hypoxia-inducible factor 1α.

to overexpress phosphoenolpyruvate carboxykinase 1 (PCK1) that supports PEP to be accrued can maintain Ca^{2+}-NFAT signaling and consequent activation [28].

Besides, many glycolytic enzymes of T lymphocytes also induce the evasion of tumor cells from immunosurveillance. In particular, as an indispensable participant in the processes of tumor progression, immune modulation, and glycolysis, remodeled pyruvate kinase isoform M2 (PKM2) enables PD-L1 to be overexpressed on T cells and tumor cells via modulating hypoxia response elements of hypoxia-inducible factor 1α (HIF-1α) target genes [105,106], which is bound to induce immune evasion of tumor cells. Secondly, diminished expressions of GLUT and hexokinase 2 (HK2) within metabolism-reprogrammed TME debilitate activated tumor infiltrating lymphocytes (TILs), which is relevant to incremental regulatory T cells (Treg cells) and expression of PD-L1 and galectin-9 on tumor cells [107]. In addition to glycolysis, T lymphocytes also reprogram the process of glycogen anabolism that is upregulated in many solid tumors, including renal, breast, bladder, uterine, ovarian, skin and cerebral tumors [108]. Specifically, glycogen synthase kinase 3 (GSK3), encoded by GSK3A and GSK3B, is the crucial rate-limiting serine/threonine phosphatase in glycogen anabolism and PD-1 overexpression in $CD8^+$ T cells [109]. Blockading GSK-3 downregulates PD-1 transcription by more than 80%, although the combination between anti-PD-1 antibody and GSK-3 blocker fails to further enhance the killing of $CD8^+$ T cells [110,111].

What is worse, the glucose-deficient TME, however, may be constructive for developing Treg cells where they primarily fuel their energy demand via fatty acid

Table 1 Immunometabolism of tumor-infiltrating immunocytes

Immunocyte	Glucose metabolism	Lipid metabolism	Amino acid metabolism
T cell			
Teff cell	Insufficient glycolysis downregulates tumoricidal effector molecule expression and triggers T cell anergy or even apoptosis [30,34] Tumor-derived lactate blunts anti-tumor immunity by varying pyruvate utilization and intercepting succinate signaling in $CD8^+$ T cells [40] Underproductive PEP is inimical to T cell immunosurveillance [28]	$CD8^+$ T cells with incremental lipid ingestion overexpress PD-1 and enhance FAO, which impedes their effector functionality [41,42] CD36 mediates FA ingestion by $CD8^+$ TILs, which engages in lipid peroxidation and ferroptosis, culminating in adynamic tumoricidal capability [43,44] Cholesterol accumulation in the cytoplasm triggers the overexpression of inhibitory checkpoints and the functional exhaustion of $CD8^+$ TILs [45]	There is too meagre Arg for T cells to mediate antineoplastic immunity, which promotes tumor growth and resistance to immunotherapy [46–49] Trp deprivation represses T cell tumoricidal immunity, and Trp-associated metabolite accruement foments tumor evasion [50] Due to the lack of Gln, Teff cells are irresponsive and Th1 and Th17 differentiation are repressed [29,51,52]. Dual lack of Asp and Gln spawns mass T cell death [53] Met starvation embodies in meager Met and SAM, defective T cell function and survival [54,55] Cys/Cys-Cys deprivation spawns T cell dysfunction and exhaustion by disrupting redox balance [56,57]
Treg cell	Foxp3 lessens glycolysis in Treg cells, which allows them to be free from lactate limitation [58] Treg cells exploit lactate within the TME to sustain immunosuppression [59]	Treg cells ingest exogenous FAs and elevate FAO to establish immunosuppression [42,60] FAS mediated by FASN is conducive to the functional maturation of Treg cells [61] SREBPs are overexpressed in Treg cells and participate in PD-1 overexpression [62]	
Tm cell		Tm cells depend upon intrinsic mobilization of FAs, utilize short- or medium-chain FAs, engage FAO to a greater extent [63–65]	
NK cell	Deprived amino acids repress mTOR signaling and glycolysis in NK cells, blunting their effector function [66] Accrued SREBP inhibitors in the TME and overexpressed FBP1 in NK cell attenuate glycolysis and then NK cell cytotoxicity [67,68] Extracellular accumulation of ADO inhibits OXPHOS and glycolysis of NK cells, which suppresses their cytotoxicity [69]	The intracellular lipid droplet accumulation profoundly inhibits NK cell cytotoxicity and metabolic bioactivity [70]	The expression of ARG1 in the TME exhausts the Arg available for the antineoplastic response of NK cells [13]
DC	Impaired glycolysis in DCs inhibits their antigen presentation, cytokine generation, T cell stimulation [71] T cells activated by DCs compete for glucose, which represses glycolytic activity of DCs [72,73] The low pH of TME accentuates mitochondrial respiration while attenuating glycolysis in DCs [74,75]	Lipid droplets accrue in DCs owing to either *de novo* FAS or intake from plasma, blunting antigen presentation [76,77] The accrued ROS in DCs oxidizes lipids and blunts presentation capability and thus T cell priming [78,79] Lipid peroxidation elicits the UPR and ER stress responses, hindering effector molecule trafficking and T cell priming [80] FAs accumulation intensifies FAO in DCs, leading tumor toward a more immunotolerant state [81] PGE2 yielded by tumor cells and intratumoral DCs impedes DC antigen presentation [82,83]	The entwined pathway between IDO1 and ARG1 in DCs leads DCs toward a more immunosuppressive state [84]
Macrophage			
M1-like TAM	In the onset inflammatory phase of tumor initiation, TAMs manifest a more glycolytic characteristic that drives TAMs toward M1-like TAMs [85–87]	FA intake and FAO are abated in M1-like TAMs, whereas FASN plays an indispensable role in the induction of M1-like TAMs [88,89]	

(*Continued*)

Immunocyte	Glucose metabolism	Lipid metabolism	Amino acid metabolism
M2-like TAM	In the later phase of tumor progression, glucose depletion and lactate accruement skew the TAMs to underscore OXPHOS, boosting M2-like TAMs expansion [85–87]	FAO and mitochondrial biogenesis in M2-like TAMs are reinforced to fuel incremental OXPHOS essential for M2-like TMAs activation [88–90]	M2-like TAMs overexpress ARG1 that speedily catabolizes Arg and then stunts T cell activation, thereby contributing to immunosuppression [91] The high expression and secretion of IDO in TAMs reinforce their M2-like polarization by yielding Kyn [92] High levels of GLS are spotted in M2-like TAMs to maintain M2-like phenotype [93]
MDSC	When MDSCs are confronted with tumor-derived factors, they upregulate glycolytic genes and ingest much glucose [94–96] The high glycolysis of MDSCs produces CIMs and nucleotides to sustain immunosuppression [97]	Enhanced exogenous lipids ingestion and FAO enhance the immunosuppressive functions of MDSCs [98] MDSCs with lipid overload have greater immunosuppressive effect on $CD8^+$ T cells [99] The cholesterol profile of MDSCs is reshaped to reinforce their immunosuppression [100]	Arg is deprived by MDSCs expressing ARG1, iNOS and CAT2, which leads T cells to fail to recognize antigens [101] The antineoplastic effects of T cells are significantly subdued by sequestering Cys by MDSCs [102] MDSCs overexpress IDO under the induction of inflammatory cytokines [103] The incremental Gln ingestion in MDSCs is chiefly utilized in glutaminolysis, thus promoting MDSC recruitment in the myeloid lineage around the TME [104]

The preceding table illustrates the metabolic reprogramming with different types of metabolism in tumor-infiltrating immunocytes. Abbreviation: Teff cell, effector T cell; Treg cell, regulatory T cell; Tm cell, memory T cell; NK cell, natural killer cell; DC, dendritic cell; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; PD-1, programmed cell death-1; PEP, phosphoenolpyruvate; mTOR, mammalian target of rapamycin; OXPHOS, oxidative phosphorylation; TILs, tumor infiltrating lymphocytes; FBP1, fructose-1,6-bisphosphatase; ADO, adenosine; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan-2,3-dioxygenase; ARG1, arginase 1; GLS, glutaminase; FAs, fatty acids; FAS, fatty acid synthesis; FASN, fatty acid synthase; FAO, fatty acid oxidation; CAT2, cationic amino acid transporter 2; TME, tumor microenvironment; ROS, reactive oxygen species; UPR, unfolded protein response; ER stress, endoplasmic reticulum stress; PGE2, prostaglandin E2; Th17, T helper 17; SREBPs, sterol regulatory element binding proteins; CIMs, carbon intermediates; iNOS, inducible NO synthase; Arg, arginine; Kyn, kynurenine; Trp, tryptophan; Gln, glutamine; Asp, asparagine; Met, methionine; SAM, S-adenosyl-methionine; Cys, cysteine; Cys-Cys, cystine; Tyr, tyrosine; IFN-γ, interferon-γ.

oxidation (FAO)-driven OXPHOS and simply express low-level GLUT1 to ingest tiny amounts of glucose [112,113]. Intriguingly, Foxp3 lessens glycolysis in Treg cells within the TME via blockading Myc, and it in turn allows them to be free from lactate restriction [58]. More significantly, Treg cells being fundamentally distinct from $CD8^+$ T cells and $CD4^+$ T cells can even exploit lactate within the TME via various metabolic enzymes (MEs) to sustain their immunosuppressive identity, although they can survive without lactate [59]. Massive Treg cells are linked to poor prognosis in multifaceted cancers, and Treg cell depletion effectively improves antineoplastic immunity [114]. The removal of Treg cells intensifies antineoplastic responses and they can be specifically targeted for augmenting anti-tumor immunity [115]. Additionally, blockading 6-phosphogluconate dehydrogenase in the oxidative pentose phosphate pathway (PPP) can induce substantial reduction of Treg cell immunosuppressive function and shift toward $CD4^+$ Th1, Th2, and Th17 phenotypes, which in turn promotes antineoplastic immunity in mice model [116].

NK cells

NK cells under resting state and short-term activation (6 h) show only low levels of both glycolysis and OXPHOS, but even at these reduced rates, the glycolytic and oxidative programs are crucial for their rapid effector responses [117]. Upon being activated over longer periods of time (> 18 h) by receptor engagement or cytokines, NK cells overexpress glucose and nutrient transporters, thereby concomitantly upregulating glycolytic enzymes to upregulate glycolysis and increasing mitochondrial mass to sustain incremental OXPHOS, with their main form of metabolism tending to glycolysis [118]. Consistent with above findings, glycolysis-derived pyruvate that enters the mitochondria of NK cells fails to engage in the TCA cycle instead to be converted to citrate and exported to the cytosol in exchange for malate via the citrate-malate shuttle (CMS), whereby ultimately generating the reduced form of nicotinamide adenine dinucleotide (NADH), which is fed into the electron transport chain fuel OXPHOS, and cytosolic NAD^+, which serves as an essential cofactor for the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) during glycolysis induction [67]. Inhibition of glycolysis or OXPHOS by oligomycin or 2-deoxyglucose (2-DG) is sufficient to reduce the production of IFN-γ and Gzms-B by activated NK cells and impair NK cytotoxicity [118]. Accordingly, metabolic reprogramming toward glycolysis and OXPHOS is a prerequisite for NK cell to display intensified anti-tumor immunity.

As a nutrient sensor, mTOR reduces when amino acids are scant, which compromises NK effector functionality by inhibiting glycolysis [6,66]. By contrast, elevated mTORC1 signaling when NK cells being activated induces the upregulation of sterol regulatory element binding protein (SREBP) transcription factors, which in turn drives the expression of critical components of the CMS (details below) [67]. Likewise, amino acids are also significant for c-Myc signaling to support NK functional responses by overexpressing glucose transporters and glycolytic enzymes as well as promoting mitogenesis to drive enhanced OXPHOS [66]. In particular, c-Myc expression is so particularly hypersensitive to glutamine (Gln) concentrations that impoverishing Gln of NK cells alone entails the loss of c-Myc protein [66]. As such, tumor-cell-mediated dispossession of amino acids within the TME represses mTOR signaling and Myc-sustained glycolysis in NK cells [66], which offers a therapeutic opportunity. CB-839, a glutaminase (GLS) inhibitor currently in clinical trials for multifarious solid tumors, inhibits Gln utilization by tumors to upswing Gln availability, thereby boosting mTOR signaling and Myc-sustained glycolysis in NK cells and so their cytotoxic capability (ClinicalTrials.gov ID: NCT02861300).

Surprisingly, CMS is a quite unique catabolic configuration maintained by SREBPs that manipulates the expression of pivotal elements of the CMS—ATP-citrate lyase and solute carrier family 25 member 1 (SLC25A1) transporter [67]. Moreover, SREBP activity is also a prerequisite for c-Myc to maximally express [119]. Thus, SREBPs are fundamental for NK cells to support elevated glycolysis and OXPHOS rates and effector functions [67]. Notably, the activation of SREBP transcription factors can be potently blockaded by cholesterol and oxysterols [120,121]. For instance, naturally occurring inhibitors of SREBPs, such as 27-hydroxycholesterol (27-HC) and 25-hydroxycholesterol (25-HC), are found to be elevated in the circulation and accrued in the TME of patients with breast, gastric and colorectal cancers [122–126]. Unsurprisingly, inhibition of SREBPs impairs cytokine generation and cytotoxicity of both *ex vivo* mouse and human NK cells and curtails anti-tumor responses in an adoptive NK cell murine model [67]. Taken together, it can be reasonably presumed that SREBPs are worth further investigating for target in synergizing with immunotherapy.

In a murine model with lung tumor, the expression of fructose-1,6-bisphosphatase (FBP1) is induced by TME-derived transforming growth factor β (TGF-β) and gradually elevated in tumor-infiltrating NK cells during tumor progression, which works as a rate-limiting enzyme in gluconeogenesis but also can bind with HIF-α to repress transcriptional activation of glycolytic genes, thereby attenuating NK cytotoxicity and cytokine production via attenuating glycolysis [68,127,128]. Fortunately, inhibiting FBP1 with MB05032 can rescue glycolysis and cytotoxicity of NK cells during tumor promotion [68]. Remarkably, FBP1 could possess tumor-suppressive functions when expressed on tumor cells [127], so maybe the systemic inhibition of FBP1 should be circumvented. Instead, it may be worthwhile to apply FBP1 inhibitors prior to cell infusion in the context of NK cell adoptive transfer. Unfortunately, so far there are no statistics involving how long the effect of FBP1 inhibition in NK cells could last, but it would be very intriguing to probe this therapeutic approach.

Among the immunosuppressive features of tumors is hypoxia, which promotes tumor cells to catalyze the catabolism of extracellular ATP into adenosine 3′-monophosphate (AMP), and AMP into adenosine (ADO) through the ectonucleotidases CD39 and CD73, with CD73 catalyzing the dephosphorylation of extracellular 5′AMP to ADO as the termination of this conversion [129]. Following this, extracellular accumulation of ADO within the TME stimulates NK cells through the ADO A_{2A} receptor ($A_{2A}R$), which inhibits the capability of OXPHOS and glycolysis in NK cells, thereby suppressing their cytotoxicity and killing of tumor cells [69]. In the mouse breast or ovarian cancer models, it is manifested that antibody therapy with anti-CD73 antibodies or CD73 shRNA in inhibiting tumor growth and metastasis is efficacious [130,131]. Recently, this anti-CD73 antibody treatment has found its way into the clinic, such as Medimmune's Oleclumab currently in phase I clinical trials, and was also shown to augment anti-tumor efficacy of anti-PD-1 and anti-CTLA-4 ICIs in preclinical models of multifarious solid tumors [132].

DCs

The energy generation, membrane integrity, and effector functionality in activated DCs can be hardly sustained without glycolysis [133]. Specifically, the impairment of glycolysis in DCs inhibits their antigen presentation, cytokine generation, T cells stimulation, and fails to power ATP for molecule redistribution of endocytic compartments via lysosome tubulation in the process of MHC II upregulation on the surface of DCs and lysosomal compartment acidification in the process of peptides loading onto MHC II [71]. As mentioned earlier, as a nutrient sensor, mTOR can also sense the divergent concentrations of glucose around dissimilar tissues. T cells activated by DCs in turn compete for glucose with DCs so that the activity of mTOR that can sustain glycolysis while inhibiting OXPHOS via inhibiting electron transfer chain by inducible NO synthase (iNOS)-derived NO is repressed in DCs [72,73]. Likewise, the low pH of TME accentuates mitochondrial respiration in DCs while attenuating their glycolysis, lactate generation, and the activity of mTORC1 that can bolster glycolysis

via accentuating the bioactivity of transcription factors c-Myc and HIF-1α [74,75]. HIF-1α, a significant element in the immune response process of DCs, induces glycolysis genes expression under hypoxia circumstance, such as GLUT1 and lactate dehydrogenase (LDH) [134]. Therefore, the intervention targeting the above impact factors of glycolysis in DCs gives opportunities to reverse the status of glycolytic inhibition and coordinate ICIs to ameliorate the immunological effect of DCs.

Macrophages

Antithetical polarization draws forth disparate glycometabolic modes in macrophages. Pro-inflammatory (so-called M1-like) tumor-associated macrophages (TAMs) preferentially consume glucose for incremental glycolysis and present double breaks on the TCA cycle generating the overaccumulation of itaconate and succinate, which sustains HIF-1α stabilization that in turn induces the transcription of glycolytic genes and downregulates the expression of mitochondrial biogenesis genes, thereby maintaining the glycolysis of M1-like TAMs [135]. They play an essential role in pathogen clearance and tumor antigen presentation. Alternatively, tolerogenic (so-called M2-like) TAMs mainly rely on OXPHOS and are commonly considered in relation to promoting immunosuppression, tumor cell extravasations, and metastasis [135].

With the unceasing advances in tumor, the glycometabolism of TAMs appears plastic since they have been demonstrated to alter in divergent stages: in the onset inflammatory phase of tumor initiation, as HIF-1α upregulates the generation of reactive nitrogen intermediates (RNI) and reactive oxygen species (ROS), TAMs manifest a more glycolytic characteristic that seems more adaptive to the hypoxic TME resulted from rapidly proliferating tumor cells, which drives TAMs toward M1-like TAMs; whereas during the later phase of tumor progression, glucose depletion and the excess accruement of lactate within the TME skew the TAMs to present an inconsistent glycometabolic mode that more underscores the OXPHOS, which disrupts the metabolic programming and signaling cascades that bolster the pro-inflammatory M1-like TAMs, thereby boosting the expansion of pro-tumorigenic M2-like TAMs that display a more immunosuppressive state [85–87]. The glycometabolic conversion delineated above progressively occurs and pushes ahead with tumor growth from early establishment to a late stably progressing stage. As noted above, the switch of polarization and function in TAMs coincides with this glycometabolic shift in TAMs.

Hence, genetic deletion of lactate dehydrogenase A (LDHA), 2-DG administration, or mTORC1 blockade has been proposed as therapeutic modalities designed to downregulate glycolysis of tumor cells, diminish lactate within the TME, and support the repolarization of TAMs into a pro-inflammatory phenotype [136]. Likewise, anti-PD-L1 immunotherapy dwindles glycolysis of tumor cells and so might collaterally engender TAMs repolarization via upswinging glucose availability [136]. Thus, the combination of the two above mentioned seems to be a more attractive therapeutic protocol, which provides a promising point of penetration for breaking immunotherapeutic resistance to ICIs.

MDSCs

When MDSCs are confronted with tumor-derived factors, they upregulate glycolytic genes and thereby ingest glucose as the greatest capability as possible across a wide array of tumor models [94–96]. The immature MDSCs can obtain heavy glucose usage within the TME [137], and correspondingly, the maturation of them is pertaining to the high glycolytic flux and TCA cycle activity while the PPP and OXPHOS activity remain at minimal levels to ensure the generation of biosynthetic precursors and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) [97]. Specifically, the high glycolysis of MDSCs produces bountiful carbon intermediates (CIMs) as well as energy-rich nucleotides, which maintain their immunosuppressive mechanisms, and NADPH, which supplies reducing power to their multitudinal biosynthesis and conduces to preserve their cellular redox ability [97]. Notably, to maintain their tolerogenic function, MDSCs also motivate NADPH oxidases (NOX) to generate abundant ROS [138]. Although the dysregulated ROS levels are toxic to most cells, MDSCs still survive despite their elevated release of ROS, which is the consequence under the modulation of both a glycolytic metabolite and the master antioxidant transcription factor Nrf2. The enhancement of glycolysis in MDSCs entails the accumulation of PEP, which is as a ROS scavenger to keep MDSCs from overproducing superfluous ROS, thereby preventing MDSCs from apoptosis caused by oxidative damage [94,139]. Analogously, Nrf2 motivated by ROS propels the antioxidant genes expression to prevent MDSCs from oxidative stress [139,140]. Besides, the activated Nrf2 modulates activation and balance between glycolysis and mitochondrial metabolism of MDSCs in murine model with a constitutively active form of Nrf2, culminating in the expansion of highly immunosuppressive MDSCs [139].

Conversely, the inhibition of glycolysis suppresses the suppressive potency of intratumoral MDSCs. For instance, inhibition of glycolysis by 2-DG dramatically inhibits the monocytic MDSCs (M-MDSCs) differentiation from their precursors within the TME [141]. Likewise, GLUT3 knockdown by siRNA remarkably actuates polymorphonuclear MDSCs (PMN-MDSCs)

apoptosis and diminishes their glucose intake, which indicates that the survival of PMN-MDSCs relies on the glucose intake by GLUT3 [142]. Mechanistically, mTOR plays a paramount role in intensifying immunosuppressive function of MDSCs in a glycolytic fashion. Given mTOR phosphorylation is strengthened in tumor-infiltrating M-MDSCs, mTOR inhibition by rapamycin can reduce the glycolysis, whereby dampening the immunosuppressive activity of M-MDSCs and subsequently hindering the tumor development [143]. Analogously, methionine enkephalin (MENK), an endogenous opioid peptide, blocks glycolysis and ROS generation of MDSCs via PI3K/AKT/mTOR pathway, which retards the progression of colon carcinoma [144]. Correspondingly, in agreement with studies from the above murine tumor models, the clinic literature indicates that metformin actually induces adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) and thereby blockades mTOR and exerts its antineoplastic efficacy via targeting glycolysis of MDSCs in tumor bearers [145,146]. Except for metformin, other hypoglycemic agents, such as phenformin and rosiglitazone, have also manifested analogous antineoplastic bioactivity [147]. Of note, co-treatment with phenformin and PD-1 antibody also generates cooperative effects in delaying tumor progression [147]. The above findings give rise to the feasibility of immunotherapy involving hypoglycemic drugs as attractive ways to selectively target MDSCs. Further studies in the co-treatment with metabolic regulation of hypoglycemic agents and ICIs will be conducive to targeting MDSCs to treat certain tumors that are refractory to monoimmunotherapies.

Lipid metabolic reprogramming and related metabolic interventions of immune cells

T cells

Enhanced lipid ingestion, storage, and adipogenesis meet the requirements for the bioactivity of rapidly proliferating tumor cells. Tumor cells can even synthesize new FAs via activating the fatty acid synthase (FASN) controlled partially by mTORC2 [148], whereas normal cells can merely ingest dietary FAs. Therefore, lipid accumulation, a trait linked to immune malfunction, is a typical metabolic alteration within the TME [43], which has varying effects on lipid metabolism of T cell subsets (Fig. 3) (Table 1).

Under normal circumstances, fatty acid synthesis (FAS) is harnessed to support Teff cell proliferation and differentiation. Unfortunately, a subset of $CD8^+$ T cells with incremental lipid ingestion overexpress PD-1 in cancer patients, which would typically repress their activity [41]. Specifically, PD-1 ligation can induce signal transducers and activators of transcription 3 (STAT3) signaling in $CD8^+$ Teff cells, which enhances FAO that in turn upregulates the expression of PD-1 and carnitine palmitoyltransferase 1A (CPT1A), a rate-limiting enzyme of mitochondrial FAO involved in the translocation of long-chain FAs from the cytosol to the mitochondrial matrix, while impeding their glycolysis and effector functionality, thereby facilitating obesity-associated breast cancer tumorigenesis and progression [42]. Fortunately, ablation of T cell STAT3 or therapy with a FAO blocker abates FAO, rallies glycolysis and $CD8^+$ Teff cell activity in obese mice spontaneously developing breast tumor, culminating in abort of breast tumor progression [42]. On the other side, the growing lipid scavenging receptors CD36 induced by cholesterol within TME mediates the ingestion of FAs by $CD8^+$ TILs, which engages in lipid peroxidation and ferroptosis, resulting in reduced cytotoxic cytokine generation and debilitated tumoricidal capability in an oxidized lipid-CD36-p38 kinase manner [43,44]. Strikingly, blockading CD36 or curbing ferroptosis in $CD8^+$ TILs can efficaciously reinstate their antineoplastic bioactivity and be endowed with higher antineoplastic efficacy in synergism with anti-PD-1 antibodies in murine models [44].

The genes involved in FAO (including CPT1A) in Treg cells are overexpressed, and the level of FAO elevates [42]. Contrary to Teff cells, Treg cells can ingest exogenous FAs and primarily count on elevated FAO to accelerate their formation, satisfy their energy needs, and build up their immunosuppressive functions [42,60]. Therefore, the incremented lipid content within the TME is conducive to further boosting immunosuppression by Treg cells [6]. Concurrently, FAS mediated by FASN is also conducive to the functional maturation of Treg cells [61]. Moreover, SREBPs play a core role in orchestrating lipid metabolism and are overexpressed in tumor-infiltrating Treg cells, which participates in PD-1 overexpression, so blocking lipid synthesis and metabolic signaling reliant on SREBPs in Treg cells can unleash effective antineoplastic immunological effect without autoimmune toxicity and even potentiate anti-PD-1 immunotherapy in mouse models [62].

The notion that T cells switch to glycolysis for effector functionality and FAO for memory formation has already been extensively acknowledged. Rather than directly ingesting extracellular FAs in $CD8^+$ TILs, memory T cells (Tm cells) depend upon intrinsic mobilization of FAs, utilize short- or medium-chain FAs whose translocation is independent on CPT1A [63,64], engage FAO to a greater extent and support the metabolic programming essential for generation and maintenance of themselves [65]. FAO acts as the metabolic energy basis for Tm cells to respond to antigen stimulation in a timely fashion and is instrumental in their mitochondria to keep normal functions and long-term cell survival [42]. Tissue-resident memory T cells (Trms), a subset of T cells that

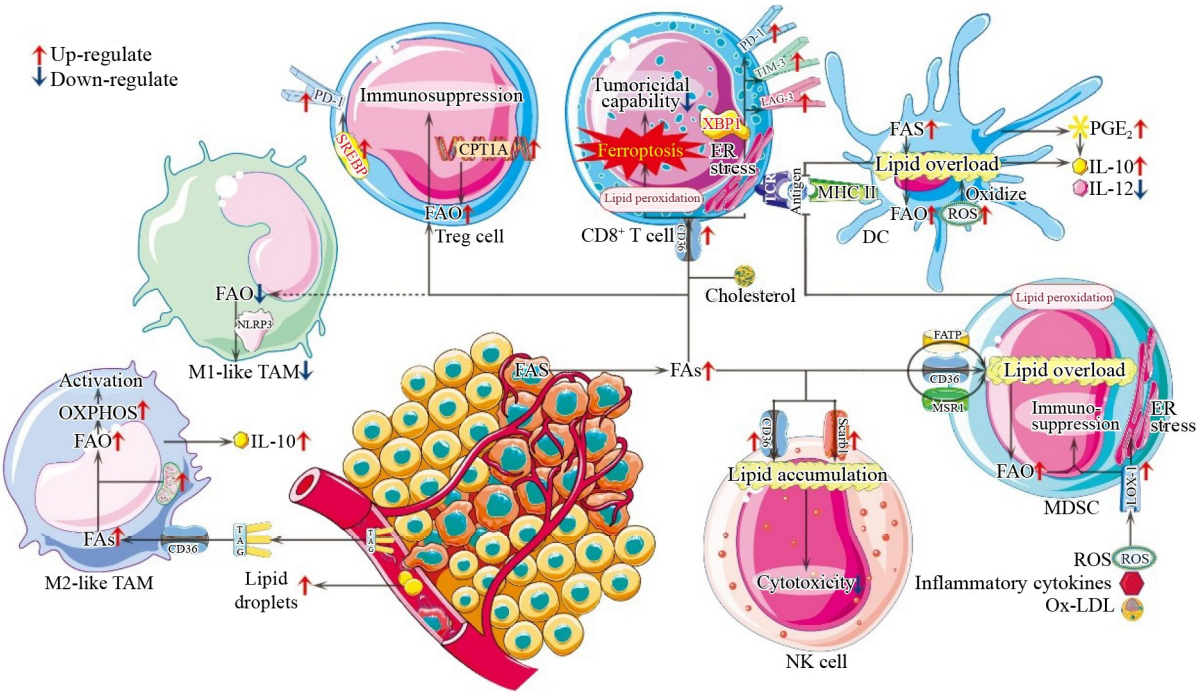

Fig. 3 Resistant mechanism of immunotherapy: lipid metabolic reprogramming of immune cells within the TME. In the TME, tumor cells interfere with immune cell function by forcing immune cells to reprogram lipid metabolism. Specifically, metabolically highly active tumor cells cause a typical metabolic alteration called lipid accumulation within the TME by augmenting FAS, which has varying effects on immune cells. In $CD8^+$ T cells, the growing CD36 mediates the ingestion of FAs, which engage in lipid peroxidation and ferroptosis, and cholesterol, which triggers the overexpression of PD-1, TIM-3, and LAG-3 in an ER stress-XBP1-dependent manner. Treg cells ingest FAs to elevate FAO, and overexpress SREBPs to further overexpress PD-1. NK cells upregulate CD36 and Scarb1 to possess lipid accumulation. The accrued ROS in DCs oxidizes bountiful lipids that accrue owing to either incremental FAS or intake from plasma. FA intake and FAO that accelerates M1-like TAMs polarization via activating NLRP3 are abated in M1-like TAMs, whereas FAO and mitochondrial biogenesis in M2-like TAMs are synchronously reinforced to fuel incremental OXPHOS essential for activation of M2-like TMAs. MDSCs enhance lipids ingestion by elevated CD36, MSR1, FATP to enhance FAO, and upregulate the LOX-1 by ROS, inflammatory cytokines and ox-LDL to induce ER stress. The lipid metabolic reprogramming ultimately emasculates the effector function of $CD8^+$ T cells, DCs, NK cells, M1-TAMs, while invigorating the immunosuppressive function of Treg cells, M2-TAMs, and MDSCs, which contributes to immunotherapy resistance. Abbreviations: PD-1, programmed cell death-1; TIM-3, T cell immunoglobulin mucin-3; LAG-3, lymphocyte activation gene 3; XBP1, X-box binding protein 1; ER stress, endoplasmic reticulumstress; SREBP, sterol regulatory element binding protein; FAO, fatty acid oxidation; CPT1A, carnitine palmitoyltransferase 1A; TAM, tumor-associated macrophage; Treg cell, regulatory T cell; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; NK cell, natural killer cell; FAS, fatty acid synthesis; ROS, reactive oxygen species; TCR, T cell receptor; PGE2, prostaglandin E2; IL-10, interleukin-10; FAs, fatty acids; OXPHOS, oxidative phosphorylation; Scarb1, scavenger receptor class B member 1; FATP, fatty acid transport protein; MSR1, macrophage scavenger receptor 1; Ox-LDL, oxidized low-density lipoprotein; LOX-1, lectin-type oxidized LDL receptor-1; TAG, triacylglycerol; NLRP3, NOD-like receptor thermal protein domain associated protein 3.

secrete higher amounts of cytokines than their circulating counterparts, construct fortified local immunity, which also has a bearing on the effectiveness of ICI immunotherapy. Instead of employing glycolysis, Trms depend on FAO for cell survival, and FA depletion leads to Trms death [149]. Targeting PD-L1 downregulates fatty acid binding protein (Fabp) 4 and Fabp5 expression in tumor cells, and the inhibition of PD-L1 upregulates Fabp4/5 expression in Trms, boosting lipid ingestion by Trms and leading to better survival [149].

Cholesterol, a critical component of membrane lipids, is necessary for TCR clustering and T cell immunological synapse to engage in the antigen-presenting, activation, and differentiation functions of TAMs and DCs [150]. But as excess cholesterol builds up in the cytoplasm, it triggers the overexpression of inhibitory checkpoints (PD-1, T cell immunoglobulin mucin-3 (TIM-3), and lymphocyte activation gene 3 (LAG-3)) in an endoplasmic reticulumstress (ER stress)-X-box binding protein 1 (XBP1)-dependent manner, which results in the functional exhaustion of $CD8^+$ T lymphocytes. Reduced cholesterol or ER stress can boost $CD8^+$ T cell antineoplastic activity in order to potentiate T cell-based immunotherapy [45]. Atorvastatin, a classic cholesterol-lowering drug, blocks the ras-activated MAPK and PI3K-Akt pathways and subsequent mTOR signaling to reduce the expression of co-inhibitory receptor and boost the release of IL-2, culminating in the ameliorated activity of activated T cells [151]. For another, because of improved T cell receptor clustering and more effective

immunological synapse formation, disrupting cholesterol esterification with an increase in plasma membrane cholesterol level has been shown to potentiate the proliferation and effector functionality of $CD8^+$ TILs, not $CD4^+$ TILs [152]. The combination of avasimibe, a blocker of the critical cholesterol esterification enzyme acylcoenzyme A cholesterol acyltransferase 1 (ACAT1) for treatment of atherosclerosis, and an anti-PD-1 antibody is more efficacious than either treatment alone at blunting tumor development in murine with melanoma, although inhibition of PD-1 fails to alter the expressions of ACAT1 and other cholesterol esterification genes [152]. Moreover, ACAT1 knockout in $CD8^+$ T cells has no adverse effect on their levels of glycolysis, OXPHOS, and FAO [152]. To sum up, manipulating cholesterol metabolism could also be harnessed to augment the tumor cytotoxicity of $CD8^+$ T cells, and the combination therapy of targeting cholesterol metabolism with ICIs still remains to be explored in greater depth.

NK cells

In certain pathological circumstances, including a murine model with lymphoma, obese individuals, and patients following cancer surgery, lipids transporters of NK cells are so highly overexpressed that FAs are excessively englobed, which is relevant to NK cells malfunction [70,153–155]. Taking murine B cell lymphoma model as an example, dysfunctional NK cells upregulate the lipid scavenging receptor CD36 as well as scavenger receptor class B member 1 (Scarb1) to possess inflated intracellular lipid droplet accumulation, which induces aberrantly elevated peroxisome proliferator-activated receptor γ (PPARγ)/PPARδ signaling associated with NK cells considerable dysfunction and has a profound inhibitory effect on NK cells cytotoxicity and metabolic bioactivity [153]. To make matters worse, in order to facilitate their progression, including proliferation, migration and evasion of immunosurveillance, tumor cells enhance lipid metabolism to enrich the TME with lipids [121,156]. Given all of that, interdicting lipids intake via suppressing CD36 bioactivity could be an efficacious approach to sustaining immune functions of NK cells in lipid-rich microenvironment. Furthermore, according to the studies reported, certain tumor cells are hypersensitive to CD36 inhibition mediated by divergent ways, such as neutralizing antibodies FA6.152 and JC63.1, and sulfo-N-succinimidyl oleate [157–160]. Hence, the application of CD36 inhibitor could be conducive to perpetuating NK cell functions while targeting tumor cells.

DCs

Lipid droplets accrue in DCs owing to either incremental *de novo* FAS or intake from plasma via the macrophage scavenger receptor 1 (MSR1) [78], which can dampen antigen presentation capability, downregulate co-stimulating molecule CD86, upregulate tolerogenic cytokine IL-10, and suppress the capacity to activate T cells [76,77]. Fortunately, administration of 5-(tetradecycloxy)-2-furoic acid (TOFA)-1, an inhibitor of acetyl-CoA carboxylase, to tumor-bearing mice normalized lipid abundance in tumor DCs and restored their capability to prime T cells [78,161].

Simultaneously, ROS also accrue in DCs owing to the hypoxic TME and NOX activity induced by pattern recognition receptors (PRRs) engagement [162]. These raised ROS oxidize the bountiful lipids, resulting in their inordinate binding to heat shock protein 70 (Hsp70). Mechanistically, this covalent binding intercepts the transport of MHC-peptide complexes to the DCs surface followed by the accruement of MHC-peptide complexes in the late endosome/lysosome [79], whereby further blunting DCs presentation capability and thus T cell priming [78]. Furthermore, lipid peroxidation elicits the unfolded protein response (UPR) and ER stress responses in DCs via inositol requiring kinase enzyme 1α (IRE1α) and XBP1 [80,163], which hinder the trafficking of effector molecules and cytokines to the DCs membrane, again intervening in T cells priming. Targeting the ER stress response is efficacious for tumor control as per pre-clinical documentation derived from *in vivo* ovarian cancer murine models and *ex vivo* patient samples. Small interfering RNAs (siRNAs) against elements of the IRE1α-XBP1 signaling pathway have been shown to diminish lipid formation in DCs infiltrating the TME, resulting in a more potent Teff cell response and improved patient survival [164].

FA accumulation also intensifies FAO in DCs, which leads tumor toward a more immunotolerant state [81]. In a murine melanoma model, DCs via the Wnt5a-β-catenin-PPARγ signaling pathway can overexpress CPT1A FA transporter protein, propel the FAO process, accelerate Tregs advancement, thwart Teff cells activation, and initiate immune privilege sites [165]. Intercepting this pathway by etomoxir, an inhibitor of FAO, can promote anti-melanoma immunity and anti-PD-1 antibody immunotherapy efficacy and curb tumor progression [165]. Moreover, Treg cells and tumor burden were mitigated when etomoxir-treated bone-marrow-derived DCs (BMDCs) were leveraged for ACT in mice [165]. Intriguingly, tumor cells secrete fat-carrying exosomes that stimulate PPARα of DCs to trigger lipid droplets synthesis in DCs and augment FAO, culminating in DCs malfunction [166]. As a crucial molecule of metabolic-immune modulation, PPARα may be exploited as an immunotherapeutic target and has a great prospect for anti-tumor treatment [166].

Additionally, prostaglandin E2 (PGE2) yielded by both tumor cells as well as tumor-infiltrating DCs is a bioactive lipid derivative derived from cyclooxygenase-catalyzed arachidonic acid metabolism, which downregulates IL-12 and MHC-II expression in DCs, while overexpressing IL-10, whereby impeding antigen presentation of DCs and attenuating Th1, $CD8^+$ T and NK cell-mediated immune responses [82,83]. Considering that cyclooxygenase 2 (COX-2) is generally absent in normal tissues but constitutively present in malignant tissues, lessening PGE2 biosynthesis with the COX-2 inhibitor NS-398 can amplify the antineoplastic potency of DCs [167].

Macrophages

FA intake and FAO are abated in M1-like TAMs, whereas FASN, a rate-limiting enzyme in FAS, plays an indispensable role in the induction of M1-like TAMs; by contrast, FAO and mitochondrial biogenesis in M2-like TAMs are synchronously reinforced to fuel incremental OXPHOS essential for activation of M2-like TMAs [88–90]. Recently, it has become clear that M2-like TAMs accrue lipids via the scavenger receptor CD36 to employ FAO instead of glycolysis for energy used for differentiation as well as tumor promotion [168]. Besides, FAO in M2-like TAMs keeps IL-10 secretion promoting tumor progression [169].

Specifically, the ingestion and lipolysis of lipids, especially exogenous triacylglycerol (TAG) yields FAs for FAO in M2-like TAMs and overexpresses the genes that define M2-like TMAs [88]. And the blockage of FAO with etomoxir can dislodge IL-4-induced M2-like TAMs polarization [88]; nonetheless, inhibiting FAO in human TAMs has no effect on IL-4 response [170], and FAO can also accelerate M1-like TAMs polarization via activating NOD-like receptor thermal protein domain associated protein 3 (NLRP3) [171]. After all, these observations indicate that the requirement for FAO in M2-like TAMs polarization is so perplexing that many issues remain to be urgently addressed. In addition, whether inhibition of FAO or augmentation of FAS upgrades the antineoplastic effect of TAMs has also yet been inconclusive [172].

Recently, modulation of TAM function by cholesterol metabolism was also documented. Intriguingly, restricting flux through the cholesterol synthetic pathway in TAMs elicits type I interferon responses to activate antiviral immunity through both autocrine and paracrine signaling [173]; that said, it remains nebulous whether the same responses could be harnessed to augment the antineoplastic effect of TAMs. Contrary to type I interferon responses, blockading ATP binding cassette transporter G 1 (ABCG1) that induces cholesterol secretion shifts TAMs from M2-like toward M1-like phenotype, whereby potentiating their tumoricidal capability *ex vivo* [174]. Hence, it remains to be clearly established how cholesterol metabolism fine-tunes TMAs behavior under diverse conditions. The resolution of this trouble will provide supporting evidence for partaking in cholesterol metabolic reprogramming to regulate host immunity and immunotherapeutic efficacy.

MDSCs

Lipid metabolism of intratumoral MDSCs is transformed to enhanced exogenous lipids ingestion from TME and FAO, accompanied by an elevation in lipid transport receptors expression (e.g., FA translocase (CD36), MSR1, and fatty acid transport protein (FATP)), mitochondrial mass, oxygen consumption rate (OCR), and FAO key enzymes expression (e.g., CPT1, acyl CoA dehydrogenase (ACADM), peroxisome proliferator-activated receptor gamma coactivator 1-β (PGC1β), and 3-hydroxyacyl-CoA dehydrogenase (HADHA)) [98]. Although the upregulation of above lipid metabolism enhances the immunosuppressive functions of MDSCs, blockage of them can efficaciously halt tumor expansion.

FATP2 is a long-chain FA transporter that is controlled by granulocyte-macrophage colony-stimulating factor (GM-CSF) and STAT5 is exclusively overexpressed both in mouse and human PMN-MDSCs but not M-MDSCs and exerts immunosuppressive potency by ingesting arachidonic acid and synthesizing PGE2, which is inhibited after the selective pharmacological inhibition of FATP2 by small molecule inhibitor lipofermata [175,176]. Lipofermata paralyses the immunosuppressive mechanism of FATP2-overexpressed PMN-MDSCs and substantially curbs tumor development in four tested tumor models [175]. Of note, in combination therapy with ICIs like anti-CTLA4 antibody, lipofermata improves the efficacy of curbing tumor development in murine on account of its highly selective targeting of MDSCs within the TME [175]. Moreover, the genetic deletion of FATP2 and CD36 suppresses the activation of oxidative metabolism and immunosuppressive capability of intratumoral MDSCs, which leads to a T cell-dependent delay in tumor development [175,177].

Unsurprisingly, in line with other myeloid cells, plentiful lipid is accrued in intratumoral MDSCs [99,178]. By comparison with MDSCs with normal lipid content, MDSCs with lipid overload have greater immunosuppressive effect on $CD8^+$ T cells [99]. Surprisingly, lipofermata can also diminish FA accruement, impede ROS release, and weaken MDSCs bioactivity, subsequently lessening tumor burden [179]. More significantly, the combination treatment of anti-PD-L1 antibody with lipofermata concomitantly abrogates immunosuppressive function of MDSCs and strengthens T cell effective capability to generate TNF-α and IFN-γ [179].

Likewise, FAO as a metabolic target on intratumoral MDSCs can optimize the efficacy of tumor immunotherapy. For instance, in the LLC mouse model, combination therapy between adoptive cell transfer and etomoxir inhibiting the rate-limiting enzyme CTP1 of FAO conspicuously weakens the immunosuppressive function of MDSCs and delays tumor progression in a T cell-dependent fashion, which is paralleled with the diminished release of immunosuppressive arginase 1 (ARG1) and ROS by MDSCs, as well as tumor-derived factors associated with MDSCs expansion (e.g., granulocyte colony-stimulating factor (G-CSF), GM-CSF, IL-6, IL-10) [98]. Besides, myeloperoxidase-driven lipid peroxidation in PMN-MDSCs might act as a possible non-cell autonomous mechanism of refraining from antigen cross-presentation by DCs [180,181]. Fortunately, inhibition of ROS and myeloperoxidase in MDSCs almost entirely expunges the peroxidized lipids, which leads to MDSCs with a diminished immunosuppressive activity [178].

Noteworthy, like tumor cells, the cholesterol profile of intratumoral MDSCs also is reshaped to reinforce immunosuppressive function of MDSCs. For instance, TME generates ROS, inflammatory cytokines and oxidized low-density lipoprotein (ox-LDL) to upregulate the MDSC surface lectin-type oxidized LDL receptor-1 (LOX-1) that serves as a new proprietary biomarker of human PMN-MDSCs with potent immunosuppressive bioactivity as well as upregulation of ER stress [100]. Besides, liver-X nuclear receptor (LXR) activation by agonism of RGX-104 has been demonstrated to promote the transcription of apolipoprotein E (ApoE) that binds with low density lipoprotein receptor-related protein 8 (LRP8) expressed on MDSCs to induce MDSCs apoptosis and depletion, culminating in tumor growth retardation and tumor volume shrinkage [182,183]. Accordingly, reprogramming cholesterol metabolic deregulation of intratumoral MDSCs is an emerging immunotherapeutic paradigm to control tumor progression.

Amino acid metabolic reprogramming and related metabolic interventions of immune cells

T cells

T cells do not express arginosuccinate synthase (ASS1) that can synthesize arginine (Arg) from ornithine (Orn), which leads them to heavily rely on extracellular Arg ingestion principally through the high affinity cationic amino acid transporter (CAT)-1 (SLC7A1) [50,184]. Unfortunately, tumor cells themselves together with tumor-associated cells like fibroblast, MDSCs, and M2-like TAMs overexpress SLC7A2 and ARG1 to transport and catabolize extracellular Arg, respectively, as an immunological tolerance mechanism that causes too meagre Arg for T cells to mediate antineoplastic immunity and thereby promotes tumor growth and resistance to immunotherapy (Fig. 4) (Table 1) [46–49]. Albeit with T cell malfunction in this instance, tumor cells can metabolically acclimate Arg depletion via overexpressing ASS1 in an ATF4 and CEBPβ-dependent way [184]. On the flip side, Arg is the only amino acid of which the intracellular concentration drops after T cell activation, which is rather the consequence of rapid catabolism of Arg into Orn by ARG2 than of restricted ingestion through CAT-1 [47]. From a therapeutic standpoint, blockading ARG within the TME can enhance Arg bioavailable for Teff cells by interdicting Arg catabolism. For instance, as a potent small-molecule blocker of ARG1, CB-1158 can relieve MDSC-mediated T cell depression *ex vivo*, raise $CD8^+$ T cells infiltration and effect within the TME, suppress tumor progression in multifarious tumor models, and synergize antineoplastic effect of ICIs in mouse models in particular [185]. This combination of CB-1158 and ICIs is being tested in a clinical trial in patients with advanced/metastatic solid tumors (ClinicalTrials.gov ID: NCT02903914). Another example is that genetic ablation of ARG2 in murine upgrades Arg levels within serum, secondary lymphoid organs, and the TME, which enhances $CD8^+$ T cell infiltration within the TME and thereby decelerates the growth of MC38 colon carcinoma and B16 melanoma [186]. T cell-specific deletion of ARG2 provokes reinforced antineoplastic response upon adoptive cell transfer, as compared to wild-type T cell adoptive transfer, an effect that is even more profound when combined with ICIs [186]. Moreover, Arg supplementation during *ex vivo* T cell expansion promotes the engagement of OXPHOS at the expenses of glycolysis and induces the differentiation of central memory-like T cells, which prolongs T cell persistence and antineoplastic response in mouse B16 melanoma model [47]. More significantly, Arg administration synergistically enhances anti-PD-L1 effect in murine osteosarcoma model [187]. Besides, the latest generated ASS1-expressing CAR-T cells are endowed with augmented *ex vivo* proliferation in addition to ameliorative tumor control and *in vivo* survival [188]. Last but not least, that certain tumors like melanoma, hepatocellular carcinoma (HCC), pancreatic cancer and glioma also merely rely on extracellular Arg for survival owing to lack of ASS1 requisite for *de novo* synthesis of Arg is an occurrence known as Arg auxotrophy [189,190], which makes the deprivation of Arg a possible way against tumor. PEGylated Arg deiminase (ADI-PEG20) catabolizes Arg into citrulline and eliminates Arg within the TME, inducing Arg auxotrophic tumor cell death through mitochondrial damage, nuclear leakage,

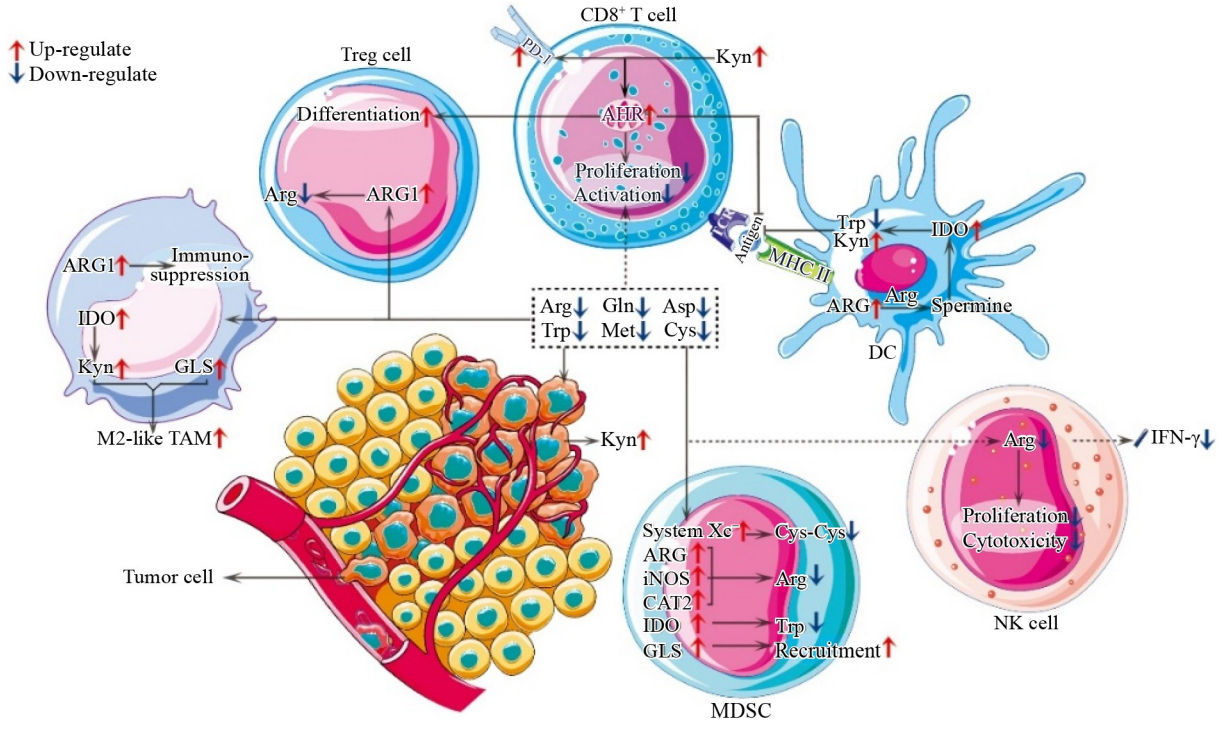

Fig. 4 Resistant mechanism of immunotherapy: amino acid metabolic reprogramming of immune cells within the TME. In the TME, tumor cells interfere with immune cell function by forcing immune cells to reprogram amino acid metabolism. Specifically, metabolically highly active tumor cells deplete large amounts of amino acids (e.g., Arg, Gln, Asp, Trp, Met, Cys), which limiting the availability of amino acid to $CD8^+$ T cells, NK cells and DCs, and generate immunosuppressive metabolites (e.g., Kyn), which can be directly transferred into $CD8^+$ T cells to overexpress PD-1 and directly activate AHR to boost Treg differentiation while blunting DC function and Teff cell proliferation. The expression of IDO and ARG1 is upregulated in DCs, leading DCs toward a more immunosuppressive state by an entwined pathway between IDO1 and ARG1. M2-like TAMs overexpress ARG1 that speedily catabolizes Arg, IDO and GLS that reinforce M2-like polarization. MDSCs overexpress ARG1, iNOS, CAT2 to deprive Arg, and IDO to deprive Trp, and system Xc^- to deprive Cys/Cys-Cys. The incremental Gln ingestion in MDSCs is primarily utilized in glutaminolysis, thus promoting the recruitment of MDSCs. The amino acid metabolic reprogramming ultimately emasculates the effector function of $CD8^+$ T cells, DCs, NK cells, M1-TAMs, while invigorating the immunosuppressive function of Treg cells, M2-TAMs, and MDSCs, which contributes to immunotherapy resistance. Abbreviation: PD-1, programmed cell death-1; IFN-γ, interferon-γ; TCR, T cell receptor; TAM, tumor-associated macrophage; Treg cell, regulatory T cell; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; NK cell, natural killer cell; Arg, arginine; Kyn, kynurenine; Trp, tryptophan; Gln, glutamine; Asp, asparagine; Cys, cysteine; Cys-Cys, cystine; Met, methionine; ARG, arginase; IDO, indoleamine 2,3-dioxygenase; GLS, glutaminase; CAT2, cationic amino acid transporter 2; AHR, aryl hydrocarbon receptor; iNOS, inducible NO synthas.

and chromatin autophagy [189,191]. The combination of anti-PD-L1 and ADI-PEG20 controls the growth of B16-F10 melanoma and CT26 colon carcinoma in murine models, along with escalated T cell activation and diminished Treg cell accumulation [192]. In a phase II randomized clinical trial, ADI-PEG20 meliorates progression-free survival in patients with Arg auxotrophic mesothelioma [193], whereas ADI-PEG20 (as a second line therapy) fails to demonstrate an overall survival benefit for patients with HCC in a phase III study [194], but the combination of ADI-PEG20 and Nivolumab is still ongoing in the clinical trial (ClinicalTrials.gov ID: NCT04965714).

Given that indoleamine-2,3-dioxygenase 1 (IDO1) and tryptophan-2,3-dioxygenase (TDO) that degrade tryptophan (Trp) into kynurenine (Kyn) are overexpressed in tumor cells, stromal cells, DCs, and TAMs within the TME [195,196], Trp catabolism spawns the deprivation of Trp bioavailability to repress T cell tumoricidal immunity as well as the accruement of Trp-associated metabolites to foment tumor immune evasion [50]. Specifically, as a Trp downstream metabolite, cumulative Kyn is directly transferred into $CD8^+$ T cells through SLC7A5 [197], SLC7A8, and SLC36A4 to overexpress PD-1 in $CD8^+$ T cells and directly activate aryl hydrocarbon receptor (AHR) [198] that boosts Treg differentiation while blunting DC function and Teff cell proliferation [199,200], stimulates TAM CD39 expression thereby hampering T cell activation [201], and is negatively correlated with cancer patient survival [202]. Hence, Trp deprivation and Trp-Kyn-AHR associated metabolites facilitate tumor immune evasion and penalize immunotherapy. To rally Trp within the TME, diverse IDO1 blockades like epacadostat, navoximod, and BMS-986205 enjoy disparate mechanism of action, either competing with Trp for the catalytic site

of IDO1 or binding irreversibly with high affinity to IDO1 [203]. Besides, dual IDO1 and TDO blockades like HTI-1090 are also in development. These blockades overturn the immunosuppressive phenotype caused by Trp catabolism in preclinical tumor models and have entered clinical assessments in conjunction with immunotherapy, among which epacadostat was evaluated in a phase III clinical trial in conjunction with pembrolizumab in unresectable or metastatic melanoma but this combination failed to reach its primary endpoint so that this trial was prematurely terminated [204]. Nevertheless, certain clinical trials are still ongoing to appraise epacadostat in conjunction with immunotherapies like ICI and cancer vaccination. For another, intercepting Kyn-AHR pathway can improve tumoricidal efficacy of adoptive T cell transfer [198], but also curb tumor progression via intensifying antineoplastic immunity [205,206]. For instance, PEG-KYNase, a recombinant enzyme that degrades Kyn into immunologically inert metabolites, has been proved curative efficacy when administrated alone or in conjunction with ICIs in multifaceted murine tumor models, which attributes to amplified tumor-infiltrating Teff cells [206]. Additionally, an engineered Kyn consuming bacterial strain lowers tumor Kyn level *in vivo* and curbs tumor growth in conjunction with anti-PD-1 antibody [207]. Furthermore, as an AHR antagonist, IDB-AHRi intercepts the nuclear translocation of AHR and overexpresses TNF-α and INF-γ in human peripheral blood mononuclear cells, but also improves $CD8^+$ T cell tumor infiltration while diminishing Treg cells, M2-like TAMs, and CT26 colon carcinoma growth in tumor-inoculated murine model [205].

Gln is another amino acid deprived by tumor cells and substantial for tumor cells to fuel the TCA cycle and biosynthesize nucleotides and proteins [208]. Unfortunately, Teff cells are totally irresponsive within Gln-deprived TME implying that T cells are void of *de novo* synthesis of Gln [29,51,209]. On the other hand, lack of Gln impedes Th1 and Th17 differentiation but does not impact Treg cells [52]. The development of Gln antagonists or GLS blockers like 6-diazo-5-oxo-L-norleucine (DON), however, has not achieved the desired results in clinical trials and many have been eventually relinquished secondary to insufferable toxicities [210], although its exposure robustly stunts tumor cell viability, proliferation, and cell cycle progression [208]. Intriguingly, while the administration of Gln antagonist DON-derivative JHU083 incapacitates tumor Gln metabolism, it enhances infiltrating $CD8^+$ T cells and skews them toward a long-lived, highly activated memory-like phenotype capable of effector functionality [208]. The reason may attribute to the less plasticity of tumor cells although T cells also undergo metabolic reprogram during suppression of Gln metabolism [208]. JHU083 could thus be one possibility to differentially regulate immunocyte and tumor cell metabolism. More importantly, JHU083 is accompanied with better efficacious regimens for triggering antineoplastic response when coupled with anti-PD-1 antibody, which hinges on concurrent, not sequential, dosing of JHU083 and anti-PD-1 antibody [208].

Asparagine (Asp) has been recognized as a significant ally of Gln in cancer metabolism in that Asp can rescue tumor cell survival in the context of compromised Gln metabolism [211,212], but also partially compensate for depleted Gln to sustain T cell survival, whereas dual deprivation of Asp and Gln spawns considerable T cell death [53]. L-asparaginase has been clinically applied in acute lymphoblastic leukemia that lacks Asp synthetase (ASNS) and depends heavily upon extracellular Asp [213]. Besides, L-asparaginase is also sensitive for extranodal NK/T cell lymphoma [214]. Unfortunately, L-asparaginase is ineffective for other solid tumors in that they overexpress ASNS to compensate for the loss of exogenous Asp [213]. To this end, asparaginases in conjunction with metformin, a blocker of the electron transport chain that diminishes the ASNS-substrate aspartate, can more efficaciously control tumor progression in tumor-inoculated murine [215], but whether this combination therapy might negatively influence T cell-mediated antineoplastic immunity is uninformed. In sharp contrast, dietary Asp deprivation is favorable for tumor progression due to restricted actuation of $CD8^+$ T cell responses in the absence of Asp [216]. Given all of that, deep-going study is essential to fully comprehend the impact of Asp availability on both tumor cells and T cells so as to ascertain a pertinent way to employ Asp metabolism in tumor therapy.

Anomalous epigenetic patterns of intratumoral T cells inextricably correlate with T cell malfunction and limited efficacy of immunotherapy [217]. For instance, intracellular methionine (Met) is prerequisite for synthesizing S-adenosyl-methionine (SAM), the universal donor for epigenetic methylation [218,219], but tumors disarrange Met metabolism in T cells: in both murine and human, the high expression of SLC43A2, a critical Met transporter, in tumor cells and the low expression of SLC43A2 in tumor-infiltrating effector $CD8^+$ T cells give rise to Met starvation that embodies by meager Met and SAM for T cells, deficient expression of dimethylation of histone H3 lysine 79 (H3K79me2) and STAT5 in $CD8^+$ T cells, decreased trimethylation of histone H3 lysine 4 (H3K4me3) in Th17 cells, and defective T cells function and survival [54,55]. Fortunately, Met supplementation can reestablish T cell immunity in multifaceted tumor-inoculated murine models and even recuperate H3K79me2 and STAT5 expression and function in $CD8^+$

T cells of colon carcinoma patients [54]. Moreover, the combination of SAM and ICIs can efficaciously inhibit melanoma by alteration of key genes and pathways implicated in cancer and immune responses as compared with monotherapy, underlying the rationale for initiating clinical trials with SAM and ICIs [220]. On the other hand, given that tumor cells overexpress SLC43A2 to avidly consume and outcompete T cells for Met, blockage of tumoral Met ingestion via knocking down SLC43A2 or administering system L inhibitor BCH in tumor-bearing mice and colon carcinoma patients can also decelerate tumor growth, boost anti-PD-L1 antibody immunotherapy, and intensify T cell antineoplastic response [54].

Extracellular cysteine (Cys) generally exists in its oxidized form—cystine (Cys-Cys), which will be instantly reduced into Cys once imported into cells [50]. Cys maintains redox balance in T cells via biosynthesizing glutathione (GSH) to buffer ROS although homocysteine from the transsulfuration pathway also functions as a biosynthetic precursor of GSH, but also Cys serves as a sulfur donor, for example, in iron-sulfur clusters that are essential elements of enzymes that constitute the electron transport chain and whereby indirectly impacts mitochondrial metabolism [56,57]. Unfortunately, tumor cells like KRAS mutant lung adenocarcinoma, pancreatic tumor and p53 mutant tumors commonly overexpress system Xc^- for Cys-Cys ingestion, causing Cys-Cys/Cys deprivation for T cells [221–223]. Besides, excessive Met expenditure by tumor-initiating cells brings about Met deprivation within the TME, thereby curtailing homocysteine generation for GSH biosynthesis of T cells to buffer ROS [224]. Analogously, MDSCs also overexpress system Xc^- but lack transporters to export Cys, resulting in further consuming Cys-Cys and limiting Cys availability for T cells, which eventually exacerbates GSH limitation and ROS accruement in T cells [102]. Over-accumulated ROS causes DNA damage and actuates cell death. To this end, replenishing N-acetylcysteine (NAC), a precursor of GSH production, can partially preclude T cell dysfunction and exhaustion via abating oxidative stress. Specifically, when adoptively transferred to B16 tumor-inoculated mice, T cells cultured in the presence of NAC manifest superior tumor control and heightened survival in comparison with T cells cultured without NAC [225]. Furthermore, NAC drives the expansion of $CD8^+$ stem cell Tm cells with survival superiority and self-renewal capability to exert robust antineoplastic functions [226], and in conjunction with formate can recover the function of Teff cells with flawed one-carbon metabolism [227]. Unlike NAC, cyst(e)inase can degrade extracellular Cys/Cys-Cys, deplete intracellular GSH and accrue ROS, culminating in cell cycle arrest and ferroptosis in multifaceted human and mouse tumor cell lines [222,228]. Intriguingly, *in vivo* cyst(e)inase as single agent excites T cell antineoplastic responsiveness in ID8 ovarian cancer murine model [229], depletes serum Cys/Cys-Cys pool and controls tumor development in both prostate and breast cancer xenografts [228]. More significantly, combinatorial treatment of cyst(e)inase and anti-PD-L1 antibody synergistically intensifies T cell-mediated antineoplastic immunity and mediates potent tumor-selective ferroptosis [229].

Tyrosine (Tyr), a proteinogenic amino acid, is intracellularly synthesized from the essential amino acid phenylalanine through phenylalanine hydroxylase, and phosphorylation of Tyr residues by protein Tyr kinases plays a pivotal role in signal transduction and T cell activation [230]. Incremented nitration of protein Tyr residues is linked to TIL dysfunction in prostate cancer, which can be reversed by blocking Arg or NOS [231].

NK cells

The reason why Arg is essential for NK cells is that Arg of low concentrations is reported to debilitate the proliferation and IFN-γ generation in the NK-92 cell line and primary human NK cells [232]. Unfortunately, the expression of ARG1 in the TME can exhaust the Arg available for the antineoplastic response of NK cells [13]. Consequently, Arg replenishment as well as prevention of Arg degradation in the TME are attractive strategies to re-invigorate NK cell-mediated immune effects [47]. On the one hand, supplementation of Arg vitalizes NK cells cytotoxicity and effector cytokine generation *ex vivo* and, in conjunction with anti-PD-L1 antibody immunotherapy, conspicuously improves antineoplastic immune effects and prolongs the survival of osteosarcoma-bearing murine [187]. On the other hand, INCB001158, a robust small-molecule inhibitor of ARG1, pushes NK cells tumor infiltration and inflammatory cytokine generation in murine tumor models and even synergistically heightens antineoplastic efficacy of ICIs in mouse models [185] and is being tested to combine with ICI pembrolizumab in a current clinical trial in patients with advanced or metastatic solid tumors (ClinicalTrials.gov ID: NCT02903914).

As previously mentioned, the main role of Gln is to sustain the signaling of other metabolic regulators, including mTOR and c-Myc, rather than to be harnessed as a fuel. Analogously, while Gln is one of the non-essential amino acids, it is also deprived in TME with rapid growth and progression of tumor cells. As for the countermeasures, see the subsection of “NK cells” in the section of “Lipid metabolic reprogramming and related metabolic interventions of immune cells” above for details.

DCs

Tumor-infiltrating DCs can express and secrete IDO, which attenuates DC function through tryptophan metabolism [233]. After decomposing Trp by IDO into metabolic intermediate Kyn, the Trp deficiency occurred topically, and the metabolite reshapes the immune status of TME. On the one hand, Kyn itself directly impairs the immune response against tumor by serving as a signaling molecule [234]. On the other hand, Kyn actuates the expression of AHR in DCs by functioning as an AHR agonist [202]. Simultaneously, as a downstream Trp metabolite of Kyn, 3-hydroxyanthranilic acid (3-HAA) activates the transcriptional bioactivity of AHR in the conventional DCs and stimulates the proliferation of Treg cell by straightforwardly targeting nuclear coactivator 7 (NCOA7) [235], while also stimulating the secretion of IDO1 in other DCs by interacting with CTLA4 [236]. Unfortunately, these resultant overexpressed AHR in turn overexpresses IDO, thereby further aggravating its immunosuppressive impact [237]. In addition, the local depletion of Trp leads to a surge in uncharged tRNA (tRNA), which results in general control non-derepressible 2 (GCN2) mediating a comprehensive stress response. Mechanistically, as a key sensing element for low concentrations of amino acids, GCN2 can be triggered to prod cell functions into free radical reprogramming under the dilemma of limited access to amino acids, culminating in immunocyte cycle arrest and autophagy [238]. Of note, Trp deprivation can also directly trigger GCN2, thereby precipitating Treg differentiation as well as constraining Teff cell functions [239].

Consistent with above findings, the antineoplastic efficacy of anti-CTLA-4 or anti-PD-L1/anti-PD-1 was dramatically elevated in IDO-scanty melanoma-bearing mice [240]. Correspondingly, finding in a preclinical model of breast carcinoma manifests that immunotherapeutic vaccination with tumor antigen-loaded, IDO-silenced DCs raises the proliferation and cytotoxic activity of antigen-specific T cells while decreasing Treg cells abundance versus IDO-expressing DCs vaccines [241]. Therefore, highly expressed IDO in DCs may be a barrier to ICI immunotherapy, and the conjunction of IDO inhibitors and ICIs may overcome the resistance induced by IDO in clinical practice. Indoximod, an inhibitor of IDO pathway, can repress mTOR activation to put the immunosuppressive impact of IDO into reverse [242]. Tyrosine kinase inhibitor (TKI), such as dasatinib, can also lower the phosphorylation level of IDO in DCs, annul the action of IDO on DCs, which chips away at Trp catabolism by blockading c-Kit [243]. Despite the inspiring primary efficacy achieved via the conjunction of IDO1 inhibitor and pembrolizumab in phase I/II clinical trials of melanoma patients, it regrettably failed to reach the endpoint in phase III trials [103]. More clinical trials of the combination treatment for multifarious malignancies are on the way [244].

Similar to IDO, ARG1 expression is also upregulated in DCs within the TME, which leads DCs toward a more immunosuppressive state. There is an entwined pathway between IDO1 and ARG1: ARG1 catabolizes Arg to generate ornithine to generate spermine that as a polyamine induces IDO1 bioactivity in DCs. Both IDO1 phosphorylation in DCs as well as the consequent activation of IDO1 signals are rigidly reliant on the anterior expression of ARG1 and the generation of ARG1-dependent polyamines that adjust DCs differentiation to IDO1-dependent immunosuppressive phenotypes via activating steroid receptor coactivator (SRC) 1 kinase endowed with IDO1-phosphorylating bioactivity [84]. Given these findings, joint modulation between ARG1 and IDO1 presents a promising target with great potential for efficacious immunotherapy.

Macrophages

High-level lactate and low pH within the TME drive the polarization of M2-like TAMs with high levels of ARG [245,246]. In turn, M2-like TAMs directly conjoin TME-nutrient availability with immune function through the overexpression of ARG1, which speedily catabolizes Arg and then stunts T cell activation via restricting the Arg-dependent expression of T cell CD3 ζ chain, whereby contributing to immunosuppression [91]. T cell metabolism, survival, and antineoplastic effect are all profoundly modulated by Arg availability [47].

Try-related pathways are also highly involved in the phenotype and function of TAMs. The high expression and secretion of IDO in TAMs also reinforce their M2-like polarization via yielding Kyn [92], stimulate Treg cell output through Try catabolite and concurrently collaborate with Arg metabolism in stunting antigen-presenting cell (APC) function, thus facilitating T and APC cell malfunction and an immunosuppressive TME [84,247]. Collectively, the above observations unveil that blockading IDO may alleviate the M2-like polarization of TAMs and thus improve antineoplastic capacity of TAMs to assist immunotherapy.

Gln metabolism is also a significant pathway for the polarization and function of TAMs. M2-like TAMs engage in elevated glutaminolysis, which reflects the relative overexpression of Gln transporters and key enzymes, as observed both in murine tumor models and primary human TAMs [85,248]. As an important modulator in phenotypic polarization and glutaminolysis of TAMs, the significant expression of glutamine synthetase (GS) induces TAMs toward a tumor-promoting M2-like

phenotype while administration of GS inhibitor makes a shift toward M1-like phenotype [249]; whereas high levels of GLS are spotted in M2-like TAMs to maintain M2-like phenotype [93]. Beyond that, GS also reportedly favors M2-like polarization via catalyzing the conversion of glutamate into Gln, at least *ex vivo* [249]. Correspondingly, the blockade of GS supports M2-like TAMs in repolarizing into their M1-like counterparts accompanied by incremental glycolytic flux and succinate availability [249], which implies the existence of a metabolic regulatory crosstalk between glucose and Gln metabolism in the modulation of TAMs functions. Intriguingly, consistent with this intrinsical interplay, glutaminolysis in M2-like TAMs depletes the Gln needed by antineoplastic T and NK cells, yet the resultant restrained α-ketoglutarate availability for TAMs epigenetic reprogramming conversely restricts murine M2-like polarization [93,250]. Likewise, the N-glycosylation-essential uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) biosynthesis is also coupled with glutaminolysis, which is prerequisite for M2-like polarization of TAMs so that dislodging N-glycosylation or depriving Gln both correspondingly represses M2-like polarization and chemokine C-C motif ligand 22 generation [250]. Additionally, in the absence of related intermediates in glutaminolysis, including glutamate and glutamic-pyruvic transaminase 2, M2-like polarization is waned [250]. Lastly, CD40-mediated Gln utilization bolsters FAO-induced pro-inflammatory and anti-tumorigenic phenotypes in TAMs by fine-tuning the NAD^+/NADH ratio via Gln-to-lactate conversion but genetic ablation of key metabolic enzymes engaging in CD40-mediated metabolic rewiring abolishes agonistic anti-CD40-induced antineoplastic responses and reeducation of M2-like TAMs, which highlights a therapeutic potential of metabolic preconditioning of M2-like TAMs before agonistic anti-CD40 treatments [251].

MDSCs

Intratumoral MDSCs overexpress ARG1 when they are stimulated by Th2 cytokines including IL-4, IL-10, IL-13, and so on, while overexpressing iNOS when they are induced by Th1 cytokines including TNF-α, IL-1, IFN-γ and so on [252]. Besides, intratumoral MDSCs also overexpress cationic amino acid transporter 2 (CAT2) to augment the intake of Arg [253]. As an element of the T cell receptor (TCR) ζ chain and a conditionally essential amino acid necessary for T lymphocytes activity, Arg is deprived by MDSCs expressing ARG1, iNOS and CAT2, which leads T cells to fail to recognize antigens and play an antineoplastic role [101]. Fortunately, INCB001158 can also remedy MDSC-induced immunosuppression of *ex vivo* T cells, thereby magnifying $CD8^+$ T cell quantities and function in the TME and controlling tumor development in multifaceted tumor models [185]. Additionally, inhibiting CAT2 also reverses the immunosuppressive effect of MDSCs [253]. Moreover, PMN-MDSCs prefer ROS yielded by impacting STAT3 and NOX2, while M-MDSCs overexpress iNOS to yield NO, which triggers T cells apoptosis by impacting STAT5. The reason why T cells suffer apoptosis is that Arg starvation mediated by iNOS and ARG1 entails T cells to stay in the G_0–G_1 phase of the cell cycle [252,254,255].

With the overexpression of the transporter SLC7A11, MDSCs lower the Cys-Cys concentrations within the TME by sequestering Cys-Cys, turn Cys-Cys into Cys essential for T cells activation and function, but also sequester the Cys [102]. What's worse, although cystathionase is capable of catalyzing Met and synthesizing Cys, T cells are still merely activated via ingesting extracellular Cys transferred by DCs due to the dearth of cystathionase as well as amino acid transporters in T cells [102]. As such, the antineoplastic effects of T cells can be significantly subdued by sequestering Cys by MDSCs [102].

MDSCs also overexpress IDO under the induction of inflammatory cytokines like IFN-γ [103]. As previously described, also as an essential amino acid, Trp is decomposed by IDO into Kyn, thereby lowering the levels of Trp and resisting T cells proliferation [256]. In addition, the metabolic intermediate Kyn can actuate immunosuppressive DCs and Treg cells [202], and act as an AHR agonist to integrate with AHR to upregulate downstream signaling and enfeeble anti-inflammatory effects [257].

Notwithstanding classification as a nonessential amino acid, Gln is still requisite to provide energy and substrates for the expansion of tumors and MDSCs. The incremental Gln ingestion in both tumor cells and MDSCs is primarily utilized in glutaminolysis that sustains the stability of transcription factor liver activator protein (LAP) crucial for the expression of G-CSF, thus promoting the recruitment of MDSCs in the myeloid lineage around the TME [104]. Consequently, targeting glutaminolysis, in addition to blocking tumor growth, has potent effects on blocking MDSCs in immunotherapy-resistant tumors. Strikingly, it is feasible for inhibiting glutaminolysis to augment the curative effects of anti-PD-1 and anti-CTLA-4 [104].

Other metabolic reprogramming and related metabolic interventions of immune cells

The roles of immunocyte metabolic reprogramming in manipulating immunocyte effector functionality are under further study. In the above, we highlight three of the most prominent metabolic reprogramming of the five major immunocytes, but it turns out that the metabolic

reprogramming of immunocytes within the TME is not just confined to the above three metabolic transitions and five immunocytes. Below, we will briefly recapitulate the other contents not covered above from the following dimensions.

In addition to the metabolic reprogramming of three major nutrient substance, on no account can we neglect the significance of nucleotide metabolic reprogramming. For instance, essential nutrient insufficiency competing with tumor cells like one-carbon unit undermines one-carbon metabolism and thus the immunity of the TME, including the activation of naïve T cells and the expansion function of Teff cells [258,259]. On the flip side, not only the aforementioned five immunocytes have metabolic reprogramming, but other immunocytes also reprogram their metabolism. In the context of tumorigenesis, the recent unfolding of metabolic plasticity in neutrophils has challenged the long-standing perspective that circulating neutrophils always preferentially engage in glycolysis and PPP to fulfill their cytotoxicity [6,260]. Tumor-elicited c-kit signaling in neutrophils actuates their employ of FAO to power consistent NADPH-dependent ROS generation that represses $CD8^+$ T cell functions [137].

In the cancer-immunity cycle, it is known to all that anti-tumor immunity chiefly relies on tumor-infiltrating effector $CD8^+$ T cells to directly kill target cells through cytotoxicity of cellular immunity [261]. Nevertheless, it is a little-known fact that once activated by antigen engagement of their B cell receptors, B cells not only differentiate into plasma cells that secrete tumor-specific antibodies but serve as APCs themselves to prime T cells and lead to T cell activation [262,263]. What a deplorable fact it is that B cells are vital players in the adaptive immune response but have been overlooked as components of ICI immunotherapy for a long time. Thus, our understanding of the metabolic rewiring in cells of the innate and adaptive arms of the immune system within the TME is increasing exponentially, whereas B cells have remained relatively understudied. In line with activated T cells, the nutrient-deficient TME can disrupt B cell activation in that activated B cells undergo metabolic rewiring that augments their glucose ingestion and amino acid utilization [264,265]. On the flip side, B cell-derived γ-aminobutyric acid (GABA) pushes monocyte differentiation into anti-inflammatory macrophages that secrete IL-10 and repress $CD8^+$ T cell killer function, but B cell deficiency or B cell-specific inactivation of the GABA-generating enzyme glutamate decarboxylase 67 augments anti-tumor responses [266]. Albeit the review by Fu *et al*. provides an updated one with the key findings in the immunometabolism of B cell [267], contrary to the fact that metabolic rewiring of T cells has become a favored strategy for tumor immunotherapy, B cells have been heavily understudied in this context, hence much more basic study is desired to unravel B cell-specific metabolic demands and effector functions in the context of TME.

One last thing to note is that metabolic remodeling of basophils, eosinophils, mast cells, etc. will be also of interest to be investigated to better understand the immunoediting within the TME.

Immunometabolic signaling pathways within the TME

For each major nutrient, the above summarizes the related metabolic reprogramming in each primary immune cell type in a separate manner. Below, we characterize the shared signaling pathways and functional consequences among the different immune cell type in order to obtain the complete functional picture of metabolic reprogramming in the complex TME.

AMPK signaling pathway

As a key molecule in the regulation of cell energy homeostasis, AMPK is activated in response to the stress of cells depleting intracellular ATP (e.g., low glucose, hypoxia, ischemia, and heat shock). AMPK is a cell energy detector in response to low ATP levels and actively regulates signaling pathways providing intracellular ATP (e.g., FAO and autophagy) [268], while negatively regulating ATP-consuming biosynthesis (e.g., gluconeogenesis, lipid and protein synthesis). Intriguingly, AMPK activation regulates anti-tumor immunity in cooperation with immune signaling and controlling energy metabolism which consequently impacts the activation and function of tumor-infiltrating immune cell. For instance, AMPK activation enhances the ingestion of FAs and glucose via fatty acid translocase (FAT/CD36) and GLUT4, respectively and enhances FAO and OXPHOS in mitochondria to elevate the intracellular ATP level, which eventually results in the immunosuppression by repressing Treg cell differentiation and function, weakening $CD4^+$ T cell activity, inducing MDSC cells and promoting the secretion of IL-1, IL-17, and IL-18 [269]. Additionally, AMPK activation also plays a significant role in T cell differentiation and functions via adjusting their energy metabolism. The above observations plainly hint that AMPK signaling regulates the balance between metabolism and immune function within the TME.

mTOR signaling pathway

From yeast to humans, mTOR is a serine/threonine protein kinase that is highly conserved and has a significant role in regulating cell growth and metabolism [270]. In fact, mTORC1 not only facilitates anabolism

such as protein and nucleic acid synthesis, but suppresses catabolism such as autophagy. In addition, it is also noteworthy that mTORC2 can be involved in Gln metabolism where it can enhance Gln ingestion via controlling its cell surface transporters through AGC kinase activation [271]. mTORC1 is activated by diverse stimuli (cytokines, glucose, oxygen, etc.), which is responsible for the overexpression of PD-L1 and the limited infiltration of Treg cells, NK cells, and T cells by promoting lipid and nucleic acid synthesis and inhibiting lipid and nucleic acid catabolism [16]. In addition, studies on melanoma have also discovered that the growth factors-induced mTORC2 activation can promote AKT expression and impact Gln metabolism, which diminishes T cell infiltration within the TME and culminates in the ICI resistance and tumor growth and progression [271]. The mTOR pathway not only directly acts on the energy metabolism of tumor cell, but it has a role by affecting immune cells. Further research is required to better understand the mechanism of the mTOR signaling pathway in various tumor cells and associated immune cells, as well as to assess the overall curative effect of mTOR inhibitors, in order to improve their application in the treatment of tumors.

ADO signaling pathway

Within a few hours of tissue damage, as well as in hypoxic tissues and the TME, the concentration of ADO in tissues elevates dramatically. It has been demonstrated that the accumulation of the nucleoside ADO within the TME represses the ability of different immune cells, such as CTLs and NK cells, to kill tumors by binding to cell surface $A_{2A}R$. The catabolism of ATP to AMP and AMP to ADO, respectively, is controlled by the ectonucleotidases CD39 and CD73, which are cell surface molecules [272]. In fact, ADO signaling through $A_{2A}R$ negatively regulates type 1 cytokines generation and increases IL-10 generation via cyclic adenosine monophosphate (cAMP)/protein kinase A and results in STAT5 dephosphorylation, culminating in decreased IL-2 receptor (IL-2R) signaling in T cells as well as the blockade of the nuclear factor kappa B (NF-κB) pathway [273]. Moreover, $A_{2A}R$ signaling promotes PD-L2 and IL-10 expression in DCs, which may enhance their ability to inhibit T cell antineoplastic responses [274]. $A_{2A}R$-mediated ADO signaling also promotes MDSC accumulation and vascular endothelial growth factor generation in murine tumors [275]. As a result, the pharmacological blockade of $A_{2A}R$ decreases angiogenesis and boosts T cell accumulation within the TME [275]. Furthermore, Treg cells co-express CD39/CD73 on the surface and generate extracellular ADO, conducing to immunosuppression within the TME in that ADO signaling pathway activation mediates the immunosuppression of Treg cells by PGE2 receptors expressed on T cells and results in the upregulation of adenylate cyclase and cAMP bioactivities [273,276,277]. Hence, inhibiting ADO biosynthesis by targeting CD39 and CD73 activity is an appealing method for boosting antineoplastic immunity.

The cyclooxygenase and PGE2 signaling pathway

PGE2 is a bioactive lipid derivative derived from cyclooxygenase-catalyzed arachidonic acid metabolism, which can elicit a wide range of biological effects linked to inflammatory disease. Contrary to COX-1, which is constitutively expressed in non-cancerous tissues, COX-2 is overexpressed in many malignancies and is significantly linked to immunosuppression and the creation of high levels of PGE2 within the TME [82]. According to preclinical research, excessive PGE2 generation boosts the growth and differentiation of Treg cells, suppresses the generation of IL-2 and IFN-γ in human T cells, and shifts activated T cells toward a phenotype that produces a high level of anti-inflammatory cytokines like IL-1, IL-4, and IL-10. PGE2 also facilitates M2-like TAMs differentiation and MDSC immunosuppression. In murine models, the abundance of PGE2 within the TME further impedes T cell infiltration by abrogating NK cell mediated recruitment of conventional type I DCs, thus conducing to immune escape [83]. Furthermore, PGE2 signaling pathway has been shown to inhibit CTL survival and function [278]. Together, these findings suggest that blockade of PGE2 generation and signaling cascades can intensify multiple facets of the anti-tumor immunity. In support of this theory, aspirin represses COX-1 and COX-2 as well as thus PGE2 synthesis, with substantial evidence supporting the potential of this agent to inhibit tumorigenesis, particularly of colorectal cancer [279]. As a selective COX-2 inhibitor, celecoxib mediates synergistic anti-tumor immune responses when combined with anti-PD-1 antibody immunotherapy in murine tumor model [280]. Up to now, many clinical trials of COX inhibitors in conjunction with ICIs have been initiate.

Conclusions

As we discussed throughout this review, not only metabolic programming of tumor cell influences the function of immune cells, but the metabolic programming of immune cells themselves could also affect their own fate, ultimately leading to the alteration of tumor immunity and immunotherapy resistance. What is emerging is a complex interplay between immunity and metabolic reprogramming, which is providing an extra dimension to our perception of immunotherapy resistance. To take full advantage of metabolic

intervention to broaden the spectra of cancers that can be effectively treated with ICIs, it is increasingly significant to develop a more precise understanding of how cancer-induced metabolic reprogramming in immune cells culminates in nonresponse or resistance to ICIs, which still requires efforts to dissect the metabolic mechanisms of tumor immune evasion and the metabolic demands of immune cells. We believe that the crux to circumvent tumor-resistance mechanisms will be the identification of combinations that target more than one immunocyte type. Continuously expanding our perceptions of immunometabolism and how the TME impacts it will open up innovative paths for optimizing tumor immunotherapy.

The rapid expansion in perceptions of immunometabolism within the TME has hinged on novel technologies for advancement. The recent reviews summarized the latest techniques that are related to immunometabolism [281–283]. Immunometabolism is rapidly becoming a systems-level science where multidisciplinary expertise is requisite for making the fullest use of new technologies. With the advancements in the size and complexity of multi-omic and other data sets, approaches to integrating information across platforms are becoming increasingly significant. Tools that enable genome-scale models of metabolism and metabolic networks have made abundant advancements in the last few years. Utilizing the outcome of such comprehensive models, one could identify strategies for modifying immunocyte function and bypassing immunotherapy resistance in the context of TME. For instance, by exploiting genome-scale metabolic models to an individual's tumor sequencing data, one could gain insights into how to develop functional Teff cells that can continue to work and synergize with ICIs within the TME, albeit the dearth of certain vital nutrients or excess immunosuppressive metabolites that cause T cell dysfunction.

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Compliance with ethics guidelines

Conflicts of interest Chaoyue Xiao, Wei Xiong, Yiting Xu, Ji'an Zou, Yue Zeng, Junqi Liu, Yurong Peng, Chunhong Hu, and Fang Wu declare that they have no conflict of interest.

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