

## REVIEW

# Metabolic regulation in the immune response to cancer

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## Abstract

Metabolic reprogramming in tumor-immune interactions is emerging as a key factor affecting pro-inflammatory carcinogenic effects and anticancer immune responses. Therefore, dysregulated metabolites and their regulators affect both cancer progression and therapeutic response. Here, we describe the molecular mechanisms through which microenvironmental, systemic, and microbial metabolites potentially influence the host immune response to mediate malignant progression and therapeutic intervention. We summarized the primary interplaying factors that constitute metabolism, immunological reactions, and cancer with a focus on mechanistic aspects. Finally, we discussed the possibility of metabolic interventions at multiple levels to enhance the

**Abbreviations:** 2-HG, 2-hydroxyglutarate;  $\alpha$ -KG,  $\alpha$ -ketoglutaric acid; ABCG1, ATP binding cassette transporter G1; acetyl-CoA, acetyl-coenzyme A; ACLY, ATP citrate lyase; AHR, aryl hydrocarbon receptor; AKT, protein kinase B; AML, acute myeloid leukemia; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; APCs, antigen presenting cells; ARG1, arginase 1; ASL, argininosuccinate lyase; ASS1, argininosuccinate synthase; ATP, adenosine triphosphate; BAR, bile acid receptor; BAs, bile acids; BFs, bacterial biofilms; BMDMs, bone-marrow-derived macrophages; BPTES, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide; CAR-T cell, chimeric antigen receptor T cell; CDK4, cyclin-dependent kinase 4; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CR, caloric restriction; CREB, cAMP response element-binding protein; CRMs, caloric restriction mimetics; CTLs, cytotoxic T lymphocytes; CXCL16, chemokine (C-X-C motif) ligand 16; DCs, dendritic cells; DI, dimethyl itaconate; DMF, dimethyl fumarate; FFAs, free fatty acids; GLS1, glutaminase 1; GPBAR1, G protein-coupled BA receptor 1; GPCRs, G protein-coupled receptors; GSH, glutathione; H3K9Ac, histone H3 acetylation at the lysine 9 residue; HDAC, histone deacetylase; HCC, hepatocellular carcinoma; HIF-1 $\alpha$ , hypoxia-inducible factor-1 $\alpha$ ; IDH1, isocitrate dehydrogenase 1; ICIs, immune checkpoint inhibitors; IDO, indoleamine 2,3-dioxygenase; IFN- $\gamma$ , interferon  $\gamma$ ; IGF1, insulin-like growth factor 1; IRG1, immunoresponsive gene 1; iTreg, induced Treg; JNK1, c-Jun N-terminal protein kinase; KA, kynurenic acid; KEAP1, Kelch-like ECH-associated protein 1; K<sup>+</sup>, potassium ions; LDHA, lactate dehydrogenase A; lncRNA, long noncoding RNA; LPS, lipopolysaccharide; MAP3K8, mitogen-activated protein kinase kinase kinase 8; MAPK, mitogen-activated protein kinase; MCTs, Monocarboxylate transporters; MDSCs, myeloid-derived suppressor cells; MMF, monomethyl fumarate; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; mtROS, mitochondrial reactive oxygen species; NAD, nicotinamide adenine dinucleotide; NFAT, nuclear factor of activated T cells; NF- $\kappa$ B, nuclear factor kappa-B; NK, natural killer; NKT, natural killer T; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; Nr2f2, nuclear factor erythroid 2-related factor 2; OXPHOS, oxidative phosphorylation; P2R, type-2 purinergic receptors; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; PKC $\theta$ , protein kinase C  $\theta$ ; PPAR, peroxisome proliferator activated receptor; PSA, polysaccharide A; PUFA, polyunsaturated fatty acid; RCC, renal cell carcinoma; ROR $\gamma$ t, retinoid-related orphan receptor- $\gamma$ t; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCFAs, short-chain fatty acids; SERCA, sarco/ER Ca<sup>2+</sup>-ATPase; SIRT, sirtuin 3; STAT, signal transducers and activators of transduction; SUCNRI, succinate receptor 1; TAMs, tumor-associated macrophages; TCA, tricarboxylic acid; TCR, T cell receptor; TDO, tryptophan 2,3-dioxygenase; Tef, effector T; TET1, Ten eleven translocation 1; TILs, tumor infiltrating lymphocytes; TLR, Toll-like receptor; TME, tumor microenvironment; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; Treg, regulatory T; VEGF, vascular endothelial growth factor; Wnt, wingless and INT-1

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efficacy of immunotherapeutic and conventional approaches for future anti-cancer treatments.

#### KEYWORDS

aging, cancer, immune response, metabolism, microbes, obesity

## 1 | BACKGROUND

Metabolism is generally described as the process through which nutrients are decomposed into energy and small molecule metabolites by biochemical reaction networks, and these products are subsequently utilized by cells to generate energy and macromolecules, including proteins, lipids, and nucleic acids, needed for survival and the maintenance of physiological functions [1]. In addition, metabolic pathways are closely related to epigenetic networks and cell signalling because metabolic profiles provide a reflection of the cellular state [2]. Therefore, metabolism plays a crucial role in maintaining cellular homeostasis and facilitating adaptation to intracellular and extracellular stimuli.

Cancer progression is a consequence of the inability of the immune system to eliminate neoplastic cells. Tumor immune escape can be induced by many factors, including the loss of antigenicity, the loss of immunogenicity, and the immunosuppressive tumor microenvironment (TME), which are orchestrated by nutrient limitation and the build-up of specific metabolites and signalling molecules [3, 4]. Tumor cells meet the needs for energy and macromolecules through significant metabolic reprogramming [5]. Moreover, the adaptability of tumor cells to a range of different hostile environments due to their metabolic flexibility further promotes their growth and metastasis [6]. Consequently, both metabolism disorders and failure of immunosurveillance to prevent malignancies are key drivers of cancer progression [6, 7].

Cellular metabolism serves a crucial function in regulating immune responses [8, 9]. Rapid and massive changes in immune cell function are involved in active immune responses, which are accompanied by substantial changes in cellular metabolism that are needed to support and, in many cases, force immune cell activation [8]. Cells can meet their particular requirements for energy and/or biosynthesis by regulating their metabolic pathways. Metabolic similarities have been observed between activated immune cells and tumor cells [10], and tumor cells are able to alter their metabolic profile to give them a survival advantage that allows them to maintain their optimal function by competing with and consuming essential nutrients or otherwise reducing the metabolic adaptabil-

ity of tumor infiltrating lymphocytes (TILs). Metabolites in the TME, in turn, also affect the differentiation and effector function of immune cells [10].

Herein, we summarize various issues regarding the functions of microenvironmental and systemic metabolites in effective immune responses to tumors. The potential therapeutic opportunities arising from understanding these metabolic avenues could be exploited to enhance anticancer immunotherapies.

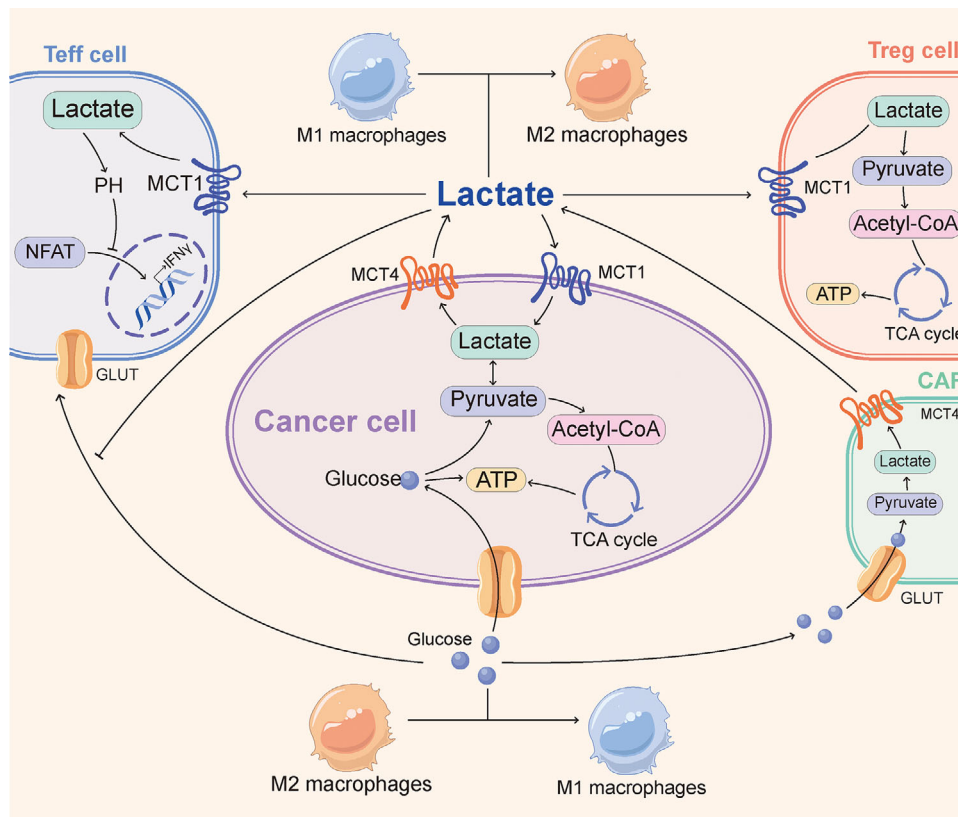
## 2 | EFFECT OF LOCAL METABOLITES ON INFILTRATING LYMPHOCYTE FUNCTION

TILs are associated with good prognosis and responsiveness to therapy [11]. Similar to cancer cells, TILs need nutrients, including glucose, lipids, and amino acids found within the TME, and utilize these nutrients in metabolic pathways, primarily glycolysis, the tricarboxylic acid (TCA) cycle, the pentose phosphate pathway, fatty acid oxidation, fatty acid synthesis, and amino acid metabolism, to support proliferation and differentiation [12]. On the one hand, cancer cells exhibit an enhanced ability to obtain nutrients, which increases the possibility of restricting nutrient consumption by TILs, thereby induces T-cell exhaustion and immune escape [3]. On the other hand, immunosuppressive cells, such as regulatory T (Treg) cells, have a symbiotic metabolic relationship with cancer cells [13]. Taken together, these findings suggest that tumor cells can outcompete neighbouring immune cells for nutrients to sustain their proliferative programmes and to restrict the activation of anticancer immune cells by simultaneously recruiting and stimulating immunosuppressive cells via the release of oncometabolites.

### 2.1 | Glucose metabolism

#### 2.1.1 | Glucose

High levels of glucose uptake and catabolism, which depend on nicotinamide adenine dinucleotide (NAD) produced by the conversion of pyruvate to lactate



**FIGURE 1** Effect of glucose and lactate metabolism on infiltrating lymphocyte function. In the TME, tumor cells consume large amounts of glucose and produce lactate. Meanwhile, tumor cells reprogram CAFs to undergo aerobic glycolysis and secrete lactate. Glucose promotes the function of Teff cells and stimulates the differentiation of macrophages into M1-like phenotype. Relatively, lactate can be metabolized by cancer cells and Treg cells to maintain energy homeostasis, stimulates macrophages to differentiate into M2-like phenotype, and inhibits T cell effector functions. Abbreviations: acetyl-CoA: acetyl-coenzyme A; ATP: adenosine triphosphate; CAFs: cancer-associated fibroblasts; GLUT: glucose transporter; IFN- $\gamma$ : interferon  $\gamma$ ; MCT: monocarboxylate transporters; NFAT: nuclear factor of activated T cells; pH: hydrogen ion concentration; TME: tumor microenvironment; TCA: tricarboxylic acid; Treg: regulatory T; Teff: effector T

catalyzed by lactate dehydrogenase A (LDHA), are required for neoplastic cell growth [1]. Studies have shown that glucose metabolism in tumor cells are partly regulated by long noncoding RNAs (lncRNAs) in different ways, including directly regulating glycolytic enzymes (such as glucose transporters, hexokinase 2, LDHA, pyruvate kinase isoenzyme M2, and pyruvate dehydrogenase kinase 1) and indirectly modulating the signaling pathways [phosphatidylinositol-3-kinase/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways and INT-1 (Wnt)/Snail pathways] [14, 15]. The rapid consumption of glucose by tumors and the relative lack of vascular supply contribute to tumor interstitial glucose concentrations being less than one-tenth that of normal organs [16], which might lead to local immunosuppression (Figure 1). Decreased glucose availability induces functional inhibition of effector T (Teff) cells.

Insufficient levels of the glycolysis metabolite phosphoenolpyruvate can increase sarco/ER  $\text{Ca}^{2+}$ -ATPase (SERCA)-mediated  $\text{Ca}^{2+}$  re-uptake, which results in

defects in  $\text{Ca}^{2+}$ -nuclear factor of activated T cell (NFAT) signalling and T cell activation [16]. In addition, reduced glucose availability leads to downregulation of interferon- $\gamma$  (IFN- $\gamma$ ) in T cells by enhancing the binding of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase to IFN- $\gamma$  transcripts and reducing histone acetylation [17], and this effect is accompanied by reduced CD4+ T cell differentiation into the Th1 phenotype [18]. Furthermore, limiting the glucose availability of Treg cells can support their growth and differentiation. The metabolic characteristics of Treg cells in the low glucose state include strengthened adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) activity, increased fatty acid oxidation, and decreased glucose oxidation and support for energy homeostasis [19, 20]. Glucose availability is also involved in macrophage regulation. An important metabolic characteristic of activated macrophages is aerobic glycolysis [21]. The differentiation of macrophages into the M1 subtype is promoted by pyruvate dehydrogenase kinase, the key enzyme of aerobic glycolysis [22], and

an enhanced glycolytic flux [23]. Thus, limiting glucose availability can inhibit macrophage activation [24]. Targeting the glucose supply in the TME yields mixed results. Reducing glycolytic metabolism by inhibiting glycolysis-regulating enzymes or using the competitive glucose, analogue 2-deoxy-D-glucose, can effectively reduce cancer cell proliferation [25] but can also inhibit the proliferation and function of Teff cells [26]. These data indicate the limitation of improving immunosuppression in the TME by targeting glycolysis, that is, the inhibition of tumor cells by targeting glycolysis might be accompanied by a decrease in TILs. Therefore, it is necessary to develop new targets that can differentially affect the glucose metabolism levels of Teff cells and tumor cells. For example, some studies have shown that acetate metabolism could enhance the function of CD8+ T cells under glucose-restricted conditions [27, 28]. An increase in the levels of the enzyme phosphoenolpyruvate carboxykinase I in tumor-specific CD4+ and CD8+ T cells increased the levels of the glycolytic intermediate phosphoenolpyruvate and thereby induced NFAT activity under glucose-limited conditions [16].

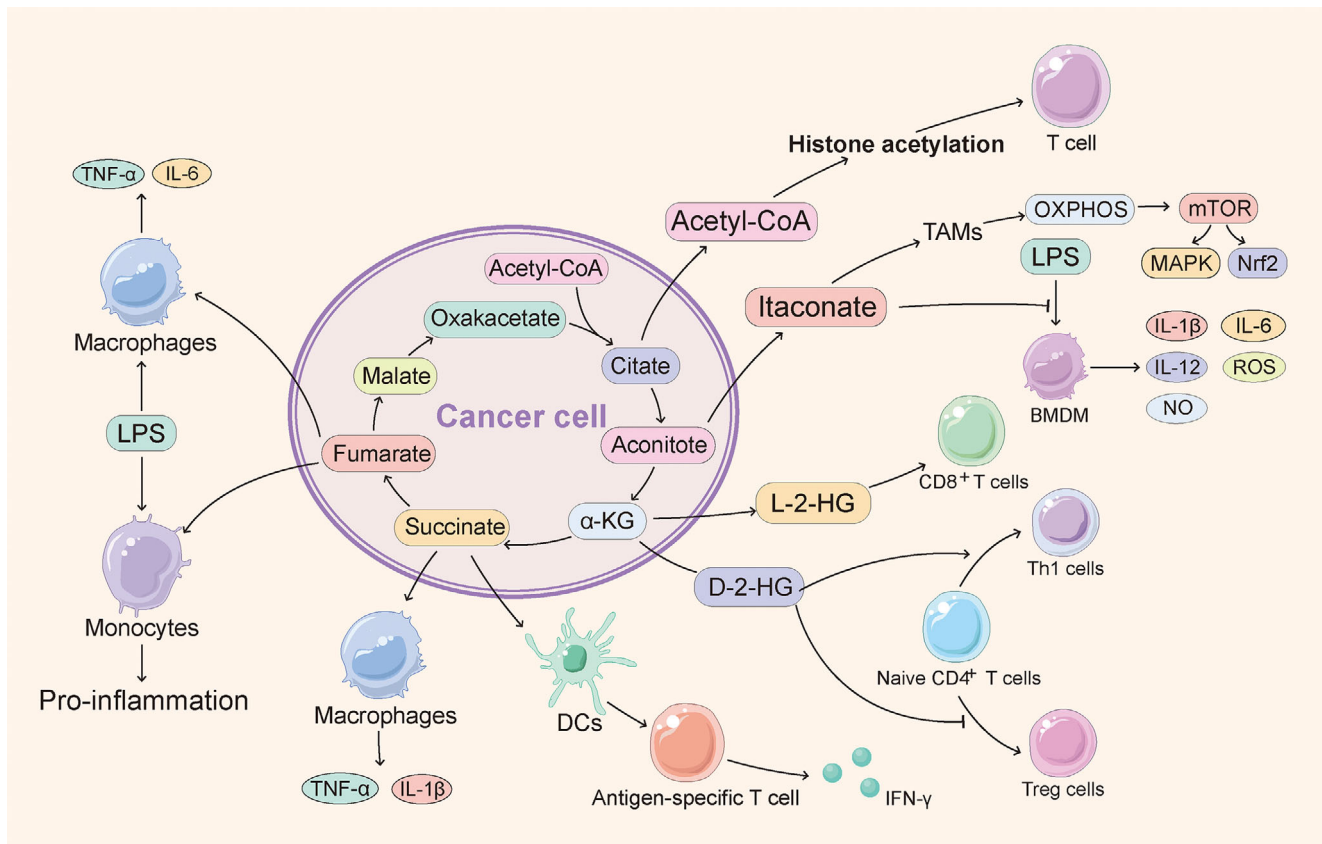
### 2.1.2 | Lactate

Lactate, a metabolic product of glycolysis, was identified as an important metabolic energy source for tumors and normal tissues in recent years [29]. High concentrations of lactate accumulate in the TME due to high glycolytic flux and decreased clearance attributed to the relative lack of a vascular supply, which increases the risk of metastasis and death [30]. Many recent studies have focused on the shuttling of lactate within tumors [31–37]. Monocarboxylate transporters (MCTs) are proteins that mediate the transport of lactate and monocarboxylate across membranes [38]. Among these transporters, MCT1 and MCT4 are closely related to tumors [33]. MCT1 is widely expressed in various tissues and promotes the uptake or efflux of lactate, depending on the cellular metabolic state and microenvironment [34]. In addition, MCT1 is usually expressed in tumor cells characterized by oxidative metabolism, particularly in cells that metabolize lactate [31]. MCT4 is only expressed in cancer or other cells, such as prostate cancer cells [35] and cancer-associated adipocytes [36], with a high glycolytic rate and is induced by hypoxia to promote the efflux of lactate [31], which indicates the important role of MCT4 in lactate efflux in the presence of a high glycolytic flux. These findings indicate that tumor cells can flexibly choose to consume or secrete lactate depending on the extracellular or intracellular concentration of lactate. Moreover, metabolic tracer studies have further validated this possibility [37]. Notably, the accumulation of lactate in the TME cannot be attributed to

cancer cells only. Recent studies have shown that cancer cells reprogrammed stromal cells (mainly cancer-associated fibroblasts) to undergo aerobic glycolysis and secrete lactate, and the secreted lactate feeds oxidative phosphorylation (OXPHOS) and mitochondrial biogenesis in cancer cells in less hypoxic regions of the TME [39, 40]. Lactate also exerts a regulatory effect on immune function. Studies showed that high concentrations of lactate induced the inhibition of glycolysis, which led to impaired function of Teff and natural killer (NK) cells [41, 42]. In contrast, high concentrations of lactate activated Treg cells because these cells could efficiently take up and metabolize lactate, particularly under low-glucose conditions [19]. Mechanistically, lactate-induced intracellular acidification prevents the upregulation of NFAT in T cells, which leads to diminished IFN- $\gamma$  production [41]. Of note, lactate is associated with not only the regulation of T cells but also the inhibition of both monocyte migration and the secretion of proinflammatory cytokines, the alteration of antigen presentation by monocyte-derived dendritic cells (DCs), and promotion of the differentiation of macrophages into the M2 subtype, particularly under hypoxic conditions [43]. Based on the abovementioned information, both LDHs and MCTs are potential targets for cancer therapy. Similarly, although the inhibition of LDH might improve the lactate levels and tumor regression, it might also lead to the inhibition of glycolysis and decreases in the numbers of T cells and the production of IFN- $\gamma$  [44, 45]. Evidence showed that MCT inhibitors could effectively alleviate acidification in the TME and reduce the rate of glycolysis in cancer while enhancing the secretion of interferon-2 (IL-2) and IFN- $\gamma$  by T cells [45, 46]. Taken together, these findings suggest that lactate might act as a selective nutrient and paracrine signalling molecule to suppress immune activity.

### 2.1.3 | TCA cycle

The TCA cycle, which serves as the hub for a variety of anabolic and catabolic functions, is an amphibolic pathway that occurs in the mitochondrial matrix. The TCA cycle is the primary oxidation pathway of acetyl-coenzyme A (acetyl-CoA) and the production pathway for the reducing equivalents nicotinamide adenine dinucleotide and flavine adenine dinucleotide. Importantly, several signalling molecules involved in the processes of immune cell activation and transformation are derived from metabolites of the TCA cycle [47]. Succinate, itaconate, fumarate, 2-hydroxyglutarate (2-HG), and acetyl-CoA can affect immune regulation and/or tumor progression by inhibiting specific enzymes or driving covalent modifications of proteins. These processes result in remodelling



**FIGURE 2** Effect of the TCA cycle on infiltrating lymphocyte function. Several signalling molecules involved in the process of immune cell activation and transformation are derived from TCA cycle metabolites, including succinate, itaconate, fumarate, 2-HG, and acetyl-CoA, which can affect immune regulation and/or tumor progression by inhibiting specific enzymes or driving covalent modification of proteins. Abbreviations: TCA: tricarboxylic acid; 2-HG: 2-hydroxyglutarate; acetyl-CoA: acetyl-coenzyme A; BMDM: bone-marrow-derived macrophage; DCs: dendritic cells; IFN- $\gamma$ : interferon  $\gamma$ ; IL: interleukin; LPS: lipopolysaccharide; mtROS: mitochondrial reactive oxygen species; mTOR: mammalian target of rapamycin; Nrf2: nuclear factor erythroid 2-related factor 2; NO: nitric oxide; OXPPOS: oxidative phosphorylation; MAPK: mitogen-activated protein kinase; ROS: reactive oxygen species; TAMS: tumor-associated macrophages; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; Treg: regulatory T;  $\alpha$ -KG:  $\alpha$ -ketoglutaric acid; Teff: effector T

of the epigenome and regulation of the expression of genes involved in immune cell effector functions and tumorigenesis (Figure 2).

Succinate accumulates in macrophages stimulated by lipopolysaccharide (LPS) and IFN- $\gamma$  and is a proinflammatory metabolite [48, 49]. The available evidence indicates that succinate plays its role as a proinflammatory effector through several pathways, including preventing hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) degradation [50] and binding to succinate receptor 1 (SUCNR1). SUCNR1 is widely expressed in different types of tissues, and high expression of SUCNR1 is found in DCs [51] and adipose tissue as well as in the liver, kidney, pancreas, and intestine [52]. The published evidence indicates that succinate, by acting as a chemokine, stimulates SUCNR1 to promote macrophage and DC migration [51]. In addition, extracellular succinate interacts with Toll-like receptor (TLR) ligands to induce the expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-1 $\beta$ , which activates the antigen presentation function

of DCs, and this activation results in further activation of T cells and increases IFN- $\gamma$  production [51]. Both the autocrine and paracrine secretion of succinate induce IL-1 $\beta$  secretion from macrophages [53]. LPS stimulation upregulates both extracellular SUCNR1 and intracellular succinate expression in macrophages, and succinate is then released from the cells, binds to SUCNR1 on the surface of surrounding cells, and exacerbates the production of IL-1 $\beta$ , which in turn further induces the expression of SUCNR1 to generate a positive feedback loop [53]. Together these data demonstrate that succinate plays an antitumor role in M1 macrophages, DCs, and Teff cells. However, succinate is a known cancer promoter that stabilizes HIF-1 $\alpha$  [50] and inhibits 2-oxo-glutarate-dependent histone and DNA demethylase [54]. Therefore, the current antitumor therapeutics targeting succinate mainly inhibit its accumulation [55].

Itaconate has emerged as an anti-inflammatory metabolite [56–58]. The available evidence showed that bone

marrow-derived macrophages (BMDMs) pretreated with dimethyl itaconate (DI), a cell-permeable methyl ester derivative of itaconate, exhibit potent inhibition of proinflammatory mediators, including reactive oxygen species (ROS), nitric oxide (NO), and the cytokines IL-1 $\beta$ , IL-12p70 and IL-6 [56]. In addition, a research showed that itaconate played an anti-inflammatory role by competitively inhibiting the succinate dehydrogenase-mediated oxidation of succinate [56]. The knockout of immunoresponsive gene 1 (IRG1), which leads to itaconate synthesis inhibition, induces BMDMs to produce more NO, IL-6, IL-12, and HIF-1 $\alpha$  in response to LPS stimulation. Moreover, IL-18 and IL-1 $\beta$  expression in IRG1<sup>-/-</sup> BMDMs is increased under conditions of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation [56]. Additional evidence also suggested that itaconate might suppress inflammation by alkylating the key redox-sensing protein Kelch-like ECH-associated protein 1 (KEAP1) and thereby the anti-inflammatory and antioxidant transcription factor nuclear factor erythroid 2 like 2 (Nrf2) [58]. Another potential mechanism of the itaconate-induced activation of Nrf2 was revealed by a study of peritoneal tumors. The production of mitochondrial reactive oxygen species (mtROS) and OXPHOS in tumor-infiltrating macrophages and the subsequent activation of mitogen-activated protein kinase (MAPK) are enhanced by itaconate, which is the main metabolic feature of M2 macrophage polarization [58]. Moreover, ROS induced by itaconate participates in the activation of Nrf2 [59]. Accordingly, Nrf2 might play a key role in the anti-inflammatory effect of itaconate. Given the anti-inflammatory effect of itaconate, this molecule is an attractive target for cancer therapy, and the available evidence showed that the downregulation of IRG1 inhibited the progression of glioma [60] and peritoneal tumors [59]. Further research is needed to develop drugs that degrade or inhibit itaconate for tumor treatment.

Fumarate has been found to be an inflammatory signal in innate immune training [61, 62]. First, the available evidence showed that after restimulation with LPS, the accumulation of fumarate in  $\beta$ -glucan-treated monocytes upregulates the secretion of cytokines, which is important for trained immunity [62]. Second, elevated fumarate levels are one of the signs of glutamine anaplerosis, which means that the shunting of glutamine into the TCA cycle is increased. Published evidence showed that the glutaminase inhibitor bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES) significantly reduced the concentrations of fumarate in the immune response induced by  $\beta$ -glucan [63]. Third, fumarate is an epigenetic regulator that inhibits  $\alpha$ -ketoglutarate-dependent dioxygenases [62]. Lysine demethylase 5 histone demethylase can be inhibited by cell-permeable fumaric acid ester monomethyl fumarate (MMF) to promote histone methylation, which

in turn increases the levels of the TNF and IL-6 promoter H3K4me3. The evidence showed that the secretion of TNF- $\alpha$  and IL-6 from macrophages after  $\beta$ -glucan training and LPS stimulation was further increased by MMF treatment [62]. These data establish a link between the TCA cycle and epigenetic regulation of the immune response [62]. In addition to trained immunity, the levels of fumarate are increased in LPS-stimulated macrophages [49]. Induction of an inflammatory argininosuccinate shunt, which establishes a link between the TCA and urea cycles, has been revealed by an integrated high-throughput transcriptional metabolic profiling and analysis pipeline (CoMBI-T) [49]. The key to this pathway is the upregulation of argininosuccinate synthase 1 (ASS1), which catalyzes the synthesis of argininosuccinate from citrulline, aspartate, and adenosine triphosphate (ATP) [64]. Combined with the fact that argininosuccinate lyase (ASL) catalyzes the cleavage of fumarate and arginine from argininosuccinate, this pathway might explain the accumulation of fumarate in macrophages. Fumarate also contributes to the regulation of T cell function through the electrophilic properties of its derivatives. Although MMF cannot suppress the activation of T cells, dimethyl fumarate (DMF) is an effective potent electrophile for relapsing-remitting multiple sclerosis (MS) and psoriasis [65]. Proteomics has revealed several proteins sensitive to the covalent modification of DMF that are involved in influencing T cell function, include protein kinase C  $\theta$  (PKC $\theta$ ) [65]. The mechanism underlying the PKC $\theta$ -CD28 interaction is impaired by DMF, and this impairment inhibits T cell activation.

2-HG is involved in tumor progression, as shown by many lines of evidence [66–69]. Mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 have been widely observed in acute myeloid leukaemia (AML) and glioma, and most of these mutations have a common mechanism of pathogenesis [66, 67], which involves alteration of the enzymatic activity to convert  $\alpha$ -ketoglutaric acid ( $\alpha$ -KG) into 2-HG by acting on several unique positions in the active site of the enzyme [70, 71]. 2-HG has two enantiomers, namely, D-2-HG (also known as R-2-HG) and L-2-HG (also known as S-2-HG). D-2-HG is mainly produced by IDH1 and IDH2 and their mutants, whereas L-2-HG is mainly synthesized by LDHA or malate dehydrogenase under acidic or hypoxic conditions [72]. 2-HG is involved in the regulation of T cells. Different metabolic remodelling processes occur during the activation of T cells to support proliferation, differentiation, and function [73]. For example, the conversion of OXPHOS to glycolysis, which is induced by HIF-1 $\alpha$  and retinoid-related orphan receptor- $\gamma$ t (ROR $\gamma$ t), is necessary for the differentiation of naive CD4<sup>+</sup> T cells into Th17 cells but is not needed for differentiation into induced Treg (iTreg) cells [74, 75]. Importantly, compared with iTreg cells, Th17 cells have

increased D-2-HG levels and are associated with increased DNA methylation levels at the forkhead box protein P3 (FOXP3) locus, which inhibits iTreg differentiation [74]. In addition, exogenous d-2-HG or the silencing of ten-eleven translocation 1 (TET1) and TET2, which regulate FOXP3 expression redundantly by demethylating the FOXP3 promoter and its intronic CpG island [76], induces the differentiation of naive CD4+ T cells into Th17 cells. Furthermore, TET1 and TET2 can be inhibited by 2-HG [74, 76]. Mechanistically, aminooxyacetic acid can inhibit glutamic-oxaloacetic transaminase 1, which can convert glutamic acid into  $\alpha$ -KG and promote the production of D-2-HG, and these effects reduce D-2-HG content and induce Th17 cell differentiation into iTreg cells [74], which indicates that D-2-HG acts as an epigenetic modifier to control T cell differentiation. In addition to D-2-HG, L-2-HG promotes the CD8+ T cell-induced elimination of tumors [77]. Similarly, CD8+ T cells rely on HIF-1 $\alpha$  and glycolysis to function in hypoxic inflammatory or tumor environments [78]. The available evidence showed that the L-2-HG levels in CD8+ T cells increased through a HIF-1 $\alpha$ -dependent pathway after T cell receptor (TCR) stimulation under physiological oxygen conditions [77]. Mechanistically, LDHA was induced by stabilized HIF-1 $\alpha$  and converts  $\alpha$ -KG into L-2-HG. L-2-HG further stabilized HIF-1 $\alpha$  and regulates the methylation of histones and DNA to alter CD8+ T cell differentiation [77]. Moreover, the proliferation, persistence, and antitumor capacity of adoptively transferred CD8+ T lymphocytes were all enhanced by L-2-HG treatment [77]. These data indicate that although 2-HG is a protumor metabolite produced by tumor metabolic reprogramming, it can also promote the antitumor immune function of T cells through HIF-1 $\alpha$  and the epigenetic pathway in the TME.

Acetyl-CoA is also a signalling molecule among metabolites involved in the TCA cycle. Acetyl-CoA is critical for histone acetylation because it is the main provider of acetyl groups in histone acetylation, which is involved in tumor progression and immunity. Thus, acetyl-CoA is involved in immune regulation. As mentioned above, glycolysis is needed for the function of T<sub>H</sub>17 cells, and studies have further elaborated the mechanism and role of acetyl-CoA in this required pathway [18]. In activated T cells, induced LDHA upregulated the acetyl-CoA flux, which promoted histone acetylation at the IFN- $\gamma$  loci and thereby increased the expression of IFN- $\gamma$ . Consistently, the lack of LDHA in T cells limited the production of IFN- $\gamma$  and the progression of autoimmune diseases in mouse models, which ultimately prevents the death of the mice [18]. Mechanistically, LDHA deficiency in T cells leads to a decrease in the levels of acetyl-coenzyme, and this effect is accompanied by a decrease in histone H3 acetylation at the lysine 9 residue (H3K9Ac) on the IFN- $\gamma$  promoter. Moreover, the expres-

sion of IFN- $\gamma$  is reduced by inhibiting ATP citrate lyase (ACLY), which converts citric acid into acetyl-CoA, and then restores the raw material for the ACL-independent synthesis pathway of acetyl-CoA under conditions of acetate supplementation [18]. In addition, ACLY is also involved in T cell growth through histone acetylation [79]. A nuclear phosphoproteomic study demonstrated that IL-2 enhanced histone acetylation and induced cell cycle regulation genes by phosphorylating ACLY. The genetic ablation or inhibition of ACLY also reduced the promotion of T cell growth by IL-2 [79]. In addition, the outcome of chemotherapy depends on Treg depletion and can be improved by hydroxycitrate, an inhibitor of ACLY [80]. Taken together, the above-described findings show that acetyl-CoA promotes T cell activation by enhancing acetylation, but the mechanism and results of its actions in other immune cells need to be further characterized.

Although succinate, fumarate, 2-HG, and acetyl-CoA exert potential proinflammatory effects in the TME, it remains difficult to translate these effects to tumor treatment. Based on metabolic similarity, these metabolites also have the effect of promoting tumor progression [55, 66, 67, 81, 82], and further studies are needed to realize the full potential of these metabolites.

## 2.2 | Lipid metabolism

Upregulated de novo fatty acid synthesis is a metabolic characteristic of neoplastic cells. This process utilizes the energy generated by glycolysis and other catabolism pathways to produce signalling molecules and plasma membrane phospholipids [83]. First, cancer-associated adipocytes [38] and cancer-associated fibroblasts [84] have been found to promote tumor progression and lipid accumulation in the TME. The available evidence showed that CD8+ TILs with high programmed death-1 (PD-1) expression levels presented both increased lipid intake and a higher lipid content and recognized tumor cells more efficiently [85]. Together, this evidence indicated the crucial role of lipid metabolism in the regulation of the tumor immune microenvironment and the feasibility of targeting lipid metabolism to regulate tumor immunity. To date, a variety of fatty acid and cholesterol metabolism inhibitors have been developed to suppress autoimmunity [86], and enhancing these metabolic pathways might also help improve antitumor immunity. The lipid composition of cell membranes is essential for TCR clustering and T cell synapses, which are involved in the activation of T cells [87]. Avasimibe, a sterol O-acyltransferase 1 inhibitor, increases the proportion of cholesterol in CD8+ TIL plasma membranes by disrupting cholesterol esterification and thereby improves T<sub>H</sub>17 cell function and promotes their

proliferation. In addition, avasimibe significantly improves the efficacy of anti-PD-1 therapy in inhibiting tumor progression and prolonging survival [88]. Similarly, drugs that increase fatty acid oxidation by activating peroxisome proliferator activated receptor (PPAR) signalling also improve the efficacy of melanoma immunotherapy [89]. Moreover, the differentiation and proliferation of different subtypes of CD4+ T cells is promoted by different fatty acids. The differentiation of proinflammatory Th1 cells and Th17 cells is promoted by the long-chain fatty acid lauric acid [90], while the development of Treg cells is supported by short-chain fatty acids [91]. Therefore, both the content and species of lipids in the TME should be considered when targeting lipid metabolism to regulate T cells. In addition to T cells, tumor-infiltrating myeloid cells, including tumor-associated macrophages (TAMs) [92], DCs [93], and myeloid-derived suppressor cells (MDSCs) [94], can take up exogenous lipids and exhibit intracellular lipid accumulation, leading to immune suppression or differentiation into anti-inflammatory subtypes. A difference in lipid metabolism has been detected between M1 and M2 macrophages: fatty acid synthesis is enhanced in M1 macrophages, whereas M2 macrophages exhibit enhanced fatty acid oxidation [95]. The published evidence showed that the silencing of mitogen-activated protein kinase kinase 8 (MAP3K8) inhibited lipid catabolism and M2 macrophage polarization [96]. In addition, the antiviral immunity of macrophages was promoted by limiting the flux of cholesterol synthesis to induce a type I interferon response [97]. However, some lines of evidence also showed that macrophages could be promoted to switch from an M2 to M1 phenotype to enhance antitumor activity by inhibiting ATP binding cassette transporter G1 (ABCG1), which mediates cholesterol efflux [98]. Therefore, how cholesterol metabolism can be targeted to regulate antitumor activity in macrophages remains to be further studied.

## 2.3 | Amino acid metabolism

### 2.3.1 | Glutamine and glutamate

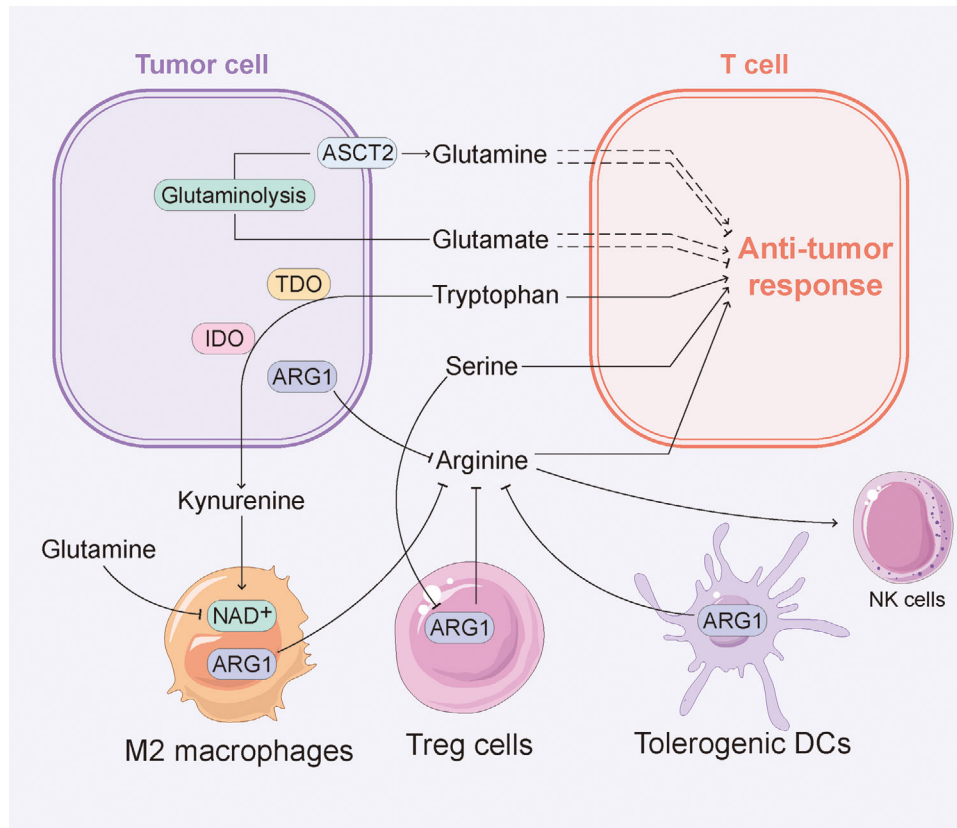
Increased glutamine intake and the decomposition of glutamine into glutamate, which depend on expression of the glutamine transporter alanine-serine-cysteine transporter 2 and glutaminase 1 (GLS1), respectively, are also metabolic characteristics of tumors [99]. Similarly, glutamine metabolism is upregulated in activated T cells and macrophages to support cell differentiation and function [100]. The removal of glutamine causes T cell proliferation arrest and prevents the secretion of IL-2 and IFN- $\gamma$  from activated T cells [100]. Additional evidence showed that

glutamine restriction inhibited Th1 cell differentiation and promotes Treg cell development [101]. However, some evidence also showed that CD8+ T cells cultured under glutamine restriction conditions were more effective in eliminating tumors *in vivo* [102], and GLS1 knock-out reduced initial T cell activation and proliferation, impairing differentiation of Th17 cells but promoting differentiation and effector functions of CD4+ Th1 and CD8+ cytotoxic T lymphocytes (CTLs) [103]. Collectively, these lines of evidence indicate that the differential effects of glutamine metabolism on different states and subtypes of T cells need to be considered when targeting glutamine to regulate immune function in the TME. Currently, treatments targeting glutamine are being tested in a clinical trial. Specifically, CB-839, an allosteric inhibitor of GLS1, can be used alone or in combination with PD-1 inhibitors to treat solid [104, 105] or hematological malignancies [106–108]. Mechanistically, the synergistic effect of CB-839 and PD-1 inhibitors might be partially attributed to the enhancement of CTL-mediated antitumor responses [103]. However, there are currently no data to indicate whether or how CB-839 inhibits tumors by affecting the immune function of the TME in patients. In addition, the glutamate levels are also involved in the regulation of T cells. Glutamate receptors are upregulated in CD4+ and CD8+ T cells in response to TCR activation and promote IFN- $\gamma$  secretion [109]. However, excessive extracellular glutamate concentrations inhibit T cell activation, and this effect is partly attributed to the inhibition of potassium currents [110]. Accordingly, the role of glutamine and glutamate metabolism in regulating immune responses in the TME needs to be comprehensively considered (Figure 3).

### 2.3.2 | Arginine

Arginine metabolism is involved in immune responses. Activated arginine catabolism through arginase 1 (ARG1) is one of the metabolic markers of the immune regulation response [111]. Immune regulatory cells, including Treg cells, tolerogenic DCs, and M2 macrophages, can degrade arginine by expressing ARG1 to limit the availability of arginine to T cells, which results in the inhibition of antitumor immune activity [112]. Arginine restriction can arrest T cells at the G0-G1 phase by inhibiting the expression of cyclin-dependent kinase 4 (CDK4) and cyclin D3 [113]. Similarly, L-arginine depletion contributes to downregulation of the TCR  $\zeta$  chain, a critical signalling element of the TCR, and thereby inhibits T cell activation [114]. It has been revealed that adaptive immunity could be suppressed by increased arginine breakdown, which was associated with enhanced Treg cell function and restricted Teff cell function [115]. Specifically, MDSCs promoted





**FIGURE 3** Effect of amino acid metabolism on infiltrating lymphocyte function. Amino acid metabolism plays a critical role in the regulation of immune response. Glutamine and glutamate metabolisms have different effects on the antitumor response of T cells under different states and of different subtypes. The removal of glutamine causes T cell proliferation arrest, while CD8+ T cells cultured under glutamine restriction conditions are more effective in eliminating tumor cells. Arginine is necessary for the activation of Teff cells. Thus, immune regulatory cells and tumor cells can degrade arginine by expressing ARG1 to limit the availability of arginine to T cells, thereby inhibiting antitumor immune activity. Tryptophan deprivation impairs the cell cycle and differentiation of T cells, and TDO and IDO, the catabolic enzymes of tryptophan, are expressed in tumor cells and various stromal cells in the TME to promote tumor progression. Serine is crucial for Teff cell response and reduces the immunomodulatory capacity of Treg cells. Abbreviations: ARG1: arginase 1; ASCT2: alanine-serine-cysteine transporter 2; DC: dendritic cell; IDO: indoleamine 2,3-dioxygenase; NAD: nicotinamide adenine dinucleotide; Teff: effector T; Treg: regulatory T; TDO: tryptophan 2,3-dioxygenase; TME: tumor microenvironment

tumor immune escape by expressing ARG1 to stabilize Treg cells and inhibit CD8+ Teff cells [116, 117]. Consistently, the published evidence showed that supplementation with arginine promoted the production of cytokines in NK cells and T cells and synergized with anti-programmed cell death-ligand 1 (PD-L1) antibodies to enhance antiimmune cell and antitumor activity [118]. In addition, the differentiation of T cells into central memory-like T cells, a type of T cell with long-term memory and stronger antitumor activity, was promoted by arginine supplementation [119], and this promotion maintained the concentration of arginine in the TME by supplementing or preventing degradation, which might represent an effective strategy to activate antitumor immunity. Specifically, INCB001158, an ARG1 inhibitor, and ADI-PEG 20, a pegylated arginine deiminase, have been applied in clinical trials in combination with pembrolizumab, an immune checkpoint inhibitor (ICI) (Table 1), and the

evidence showed that the tumor infiltration and cytokine secretion of CD8+ Teff cells and NK cells was promoted by INCB001158 *in vivo* [120] and that ADI-PEG 20 inhibited arginine auxotrophic tumors, including small-cell lung cancer [121] and breast cancer [122] by reducing the arginine levels. Notably, the evidence showed that ADI-PEG 20 treatment activated T cells, induced T cell infiltration into tumors, modulated T cell exhaustion, and reduced Treg cell accumulation [123]. Thus, the specific mechanisms of treatments that target arginine metabolism need to be further explored prior to its application.

### 2.3.3 | Tryptophan

Tryptophan is a common hallmark of the immunological TME at the clinical presentation of cancer. First, tryptophan deprivation impairs the cell cycle and the

TABLE 1 Clinical trials of INCB001158 and ADI-PEG 20 in cancer therapy

ClinicalTrials.gov Identifier	Intervention/treatment	Condition or disease	Phase
NCT03837509	INCB001158 (ARG1 inhibitor) Daratumumab SC (CD38 inhibitor)	Relapsed or Refractory Multiple Myeloma	I/II
NCT03910530	Retifanlimab (PD-1 inhibitor) INCB001158 (ARG1 inhibitor)	Advanced Solid Tumors Metastatic Solid Tumors	I
NCT03361228	INCB001158 (ARG1 inhibitor) Epacadostat (IDO1 inhibitor) Pembrolizumab (PD-1 inhibitor)	Solid Tumors	I/II
NCT02903914	INCB001158 (ARG1 inhibitor) Pembrolizumab (PD-1 inhibitor)	Metastatic Cancer Solid Tumors Colorectal Cancer Gastric Cancer Head and Neck Cancer Lung Cancer Renal Cell Carcinoma Bladder Cancer Urothelial Cancer Mesothelioma	I/II
NCT03498222	Atezolizumab (PD-L1 inhibitor) Pemetrexed Carboplatin ADI PEG20 (pegylated arginine deiminase)	Carcinoma Non-Small-Cell Lung Cancer	I
NCT03922880	ADI PEG20 (pegylated arginine deiminase) Nivolumab (PD-1 inhibitor) Ipilimumab (CTLA-4 inhibitor)	Uveal Melanoma	I

Abbreviations: ARG1: arginase 1; CTLA-4: cytotoxic T lymphocyte-associated antigen-4; PD-1: programmed death 1; PD-L1: programmed cell death-ligand 1.

differentiation of T cells. Recent evidence showed that tryptophan deprivation induced the arrest of T cells at the mid-G1 phase and makes these cells more prone to the induction of apoptosis through Fas-induced and other signalling pathways [124]. Additionally, tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), the catabolic enzymes of tryptophan, are expressed in tumor cells and various stromal cells in the TME [125]. These enzymes were reported to promote tumor progression and are associated with shorter survival [111]. TDO and IDO reduce the levels of tryptophan in the TME to inhibit the activity of CTLs [126], and the catabolite kynurenine further promotes differentiation of Treg cells and inhibits Teff cells [127], which results in the induction of tumor immune escape. Moreover, kynurenine and its downstream catabolite kynurenic acid (KA) are natural aryl hydrocarbon receptor (AHR) agonists. AHR signalling regulates immunity and will be detailed in the following paragraphs. Furthermore, kynurenine production promotes NAD synthesis and mitochondrial OXPHOS in macrophages to activate phagocytosis and anti-inflammatory effects. Furthermore, the inhibition of IDO suppresses the function of M2 macrophages [128]. In addition, a series of lines of evidence have revealed the inhibitory effect of IDO on antitumor immunity *in vivo*.

Compared with treatment consisting of antigen-loaded DCs without IDO silencing, the introduction of antigen-loaded DCs with IDO silencing into breast tumor-bearing mice enhanced tumor antigen-specific T cell proliferation and CTL activity, which reduced the number of Treg cells [129]. IDO inhibitors suppressed metastatic liver tumors and bladder tumors in mouse models by promoting tumor infiltration of neutrophils and T cells as well as the secretion of IL-12 and IFN- $\gamma$  [130]. IDO inhibitors inhibited the recruitment of MDSCs by reducing the number of Treg cells and diminishing their immunomodulatory effects in mouse models and humans with melanoma [131]. A series of IDO inhibitors and TDO inhibitors have been developed and used in different clinical trials (Table 2), and these include indoximod (IDO1 and IDO2 inhibitor), navoximod (IDO1 inhibitor), HTI-1090 and DN1406131 (IDO1/TDO dual inhibitor). Specifically, indoximod has been combined with the anti-PD-1 antibody nivolumab (NCT02073123) or pembrolizumab (NCT03301636) or the anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody ipilimumab (NCT02073123) in clinical studies to treat melanoma. The results of a phase Ib study (NCT02073123) showed that indoximod combined with ipilimumab exhibits no dose-limiting toxicity [132]. In addition, indoximod has been combined with

TABLE 2 Clinical trials testing IDO inhibitors and TDO inhibitors in cancer therapy

ClinicalTrials.gov Identifier	Intervention/treatment	Condition or disease	Phase
NCT02073123	Indoximod (IDO inhibitor) Ipilimumab (CTLA-4 inhibitor) Nivolumab (PD-1 inhibitor) Pembrolizumab (PD-1 inhibitor)	Metastatic Melanoma Stage III Melanoma Stage IV Melanoma	I/II
NCT03301636	Pembrolizumab (PD-1 inhibitor) Nivolumab (PD-1 inhibitor) Indoximod (IDO inhibitor)	Melanoma	II/III
NCT02460367	Docetaxel Tergenpumatucl-L (Lung cancer vaccine) Indoximod (IDO inhibitor)	Non-small Cell Lung Cancer Progression of Non-small Cell Lung Cancer Recurrent Non-small Cell Lung Cancer	I
NCT01302821	Adenovirus-p53 transduced dendritic cell vaccine 1-Methyl-D-tryptophan (IDO inhibitor) Carbon C II alpha-methyltryptophan	Breast Cancer	Not applicable
NCT01042535	Adenovirus-p53 transduced dendritic cell vaccine 1-Methyl-D-tryptophan (IDO inhibitor) Laboratory biomarker analysis	Male Breast Cancer Recurrent Breast Cancer Stage IV Breast Cancer Unspecified Adult Solid Tumor, Protocol Specific	I/II
NCT01560923	Indoximod (IDO inhibitor) Sipuleucel-T (Prostate cancer vaccine)	Metastatic Prostate Cancer	II
NCT02471846	Atezolizumab (PD-L1 inhibitor) GDC-0919 (IDO inhibitor)	Solid Tumor	I
NCT03491631	SHR9146 (IDO/TDO inhibitor) SHR-1210 (PD-1 inhibitor) Apatinib (tyrosine kinase inhibitor)	Solid Tumor, Metastatic Cancer, Malignant Neoplasm	I
NCT02752074	Pembrolizumab (PD-1 inhibitor) Epcadostat (IDO inhibitor)	Melanoma	III

Abbreviations: CTLA-4: cytotoxic T lymphocyte-associated antigen-4; IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; PD-1: programmed death 1; PD-L1: programmed cell death-ligand 1.

therapeutic anticancer vaccines across several tumor types (NCT02460367, NCT01302821, NCT01042535 and NCT01560923). Navoximod (NCT02471846) and HTI-1090 (NCT03491631) have been combined with the anti-PD-L1 antibodies atezolizumab and camrelizumab, respectively. Furthermore, phase I–III clinical trials of epacadostat (an IDO1 selective inhibitor) in combination with ICIs are currently in progress [133]. However, compared with pembrolizumab plus placebo, epacadostat combined with pembrolizumab did not improve progression-free survival and is unlikely to improve overall survival in patients with unresectable or metastatic melanoma in the phase III ECHO-301/KEYNOTE-252 trial [134]. Because upregulation of IDO and TDO expression is induced by chronic inflammation in the TME and is involved in immunosuppression, the immune status in the TME might partially determine the therapeutic effect of IDO or TDO inhibitors combined with ICIs. Therefore, evaluating the expression of IDO and TDO in tumors and the inflammatory state of the TME before treatment might serve as a strategy for improving the efficacy of targeted tryptophan metabolism.

### 2.3.4 | Serine

Serine, a crucial non-essential amino acid for cell growth and survival [135], participates in the synthesis of cell membranes, muscle, and nerve sheaths. As a precursor of many essential biomacromolecules such as phospholipids, ATPs, and nucleic acids, serine is reportedly needed for rapidly propagating cells [136, 137]. Furthermore, it has been found that the pathways of serine uptake and synthesis are usually upregulated in cancers, which indicates the dependence of tumor growth on serine. Similar to tumor cells, proliferating immune cells *in vitro* and *in vivo* are highly dependent on the serine supply [138]. Some key regulators that can mediate serine synthesis and metabolism also affect the growth, proliferation, and differentiation of immune cells [138–140]. Thus, both tumor cells and immune cells need an abundant supply of serine, which implies that immune cells compete with tumor cells for limited serine resources during the antitumor immune response. Rapidly proliferating T<sub>H</sub>1 cells need a serine supply both *in vitro* and *in vivo* [138].

In response to stimulation by tumor-specific antigens, primordial T cells transform into an active state characterized by rapid proliferation to generate a Teff cell pool that can mediate antitumor immunity. The activation of Teff cells requires the heavy consumption of various nutrient factors, including serine, to support their proliferative demands and exert their effector functions. Similarly, dietary serine restriction can limit T cell proliferation *in vivo* [138]. In addition, glutathione (GSH) is composed of cysteine, glutamine, and glycine and is synthesized by glutathione synthase and glutamate cysteine ligase (GCL). It has been found that GSH synthesis could be activated by serine, and the synthesized GSH then entered the one-carbon metabolic network, which is crucial for the Teff cell response [141]. GCL consists of two subunits, Gclc and Gclm. Gclc deficiency in Treg cells increased the levels of serine metabolism in Treg cells with FOXP3 downregulation, which led to activated autoimmunity and antitumor immunity in mice, and the restriction of cellular serine in Gclc-deficient Tregs restored FOXP3 expression and was crucial for maintaining the immunomodulatory capacity of Tregs both *in vitro* and *in vivo* [142]. This finding suggests that the uptake and synthesis of serine are affected by the disruption of GSH synthesis, and this feedback loop is crucial to the immunomodulatory capacity of Treg cells. In addition to T cells, serine availability is also vital to macrophages. Both NADPH produced by the pentose phosphate pathway [23] and the maintenance of intracellular reduced glutathione pools [143] are needed by M1 macrophages to neutralize ROS generated during respiratory bursts. Because serine metabolism is involved in the maintenance of NADPH and glutathione, tumor cells can induce excessive accumulation of ROS in M1 macrophages in the TME to toxic levels through the excessive consumption of serine during the chronic antitumor response [143]. Therefore, for tumor cells and activated immune cells, it is necessary to mobilize pathways of serine acquisition to meet their demand for serine, which is the theoretical basis for intervening in antitumor immunity from the perspective of serine metabolism.

## 2.4 | ATP and adenosine signalling

ATP, the energy currency of cells, and its derivatives serve as biochemical constituents involved in the function of immunomodulation in the TME [144, 145]. Intracellular nucleotides are released into the extracellular space to activate immune responses when cells undergo apoptosis or stimulation, including chemical stress, mechanical damage, hypoxia, and cytotoxic agents [146]. ATP is released through a variety of methods, including pannexin channels [147], connexin hemichannels [148], exocytosis [149],

and transmembrane transport via ATP-transporters specific for the ATP-binding cassette family, such as the cystic fibrosis transmembrane conductance regulator [150]. Furthermore, the available evidence showed that compared with autophagy-competent tumor cells, autophagy-deficient tumor cells released less ATP after treatment with antitumor chemotherapy, which suggested that autophagy was crucial for antitumor chemotherapy-induced ATP release [151].

ATP binds to type-2 purinergic receptor (P2R) family receptors, including ionotropic P2XR and metabotropic P2YR purinergic receptors [152]. ATP that originates from dying cells promotes chemotaxis and the recruitment of antigen-presenting cells (APCs) by ligating purinergic receptors of the P2RY2 and P2RX7 types [152], whereas ATP that originates from immunogenic cell death released via the autophagy-dependent pathway interacts with P2RX7 in synergy with its metabolites to recruit and activate DCs [153, 154]. The activation of purinergic signals further activates the NLRP3 inflammasome, resulting in the proteolytic activation of caspase-1 and promoting the processing and immunostimulatory release of IL-1 $\beta$ , which leads to the activation of IL-17-producing  $\gamma\delta$  T cells [155].

In the extracellular space, ATP is gradually decomposed by the nucleotidases CD39 and CD73 into adenosine, which exerts immunosuppressive effects [156]. Adenosine activates the protein kinase A signalling cascade by ligating four G protein-coupled purinergic type 1 receptors, namely A1R, A2AR, A2BR, and A3R, to enhance the activity of adenylyl cyclase-mediated production of cAMP. The levels of extracellular nucleotides can be regulated by hypoxia. Specifically, the expression of CD39 and CD73 can be elevated by hypoxia through a HIF-1-dependent pathway [157]. Hypoxia also inhibits the expression of equilibrative nucleoside transporters (ENTs), which reduces the uptake of adenosine and thereby increases the level of extracellular adenosine [158]. High levels of CD39 and CD73 are associated with poor prognosis in many human malignancies [159, 160], whereas the ecto-nucleoside triphosphate diphosphohydrolase inhibitor polyoxometalate-1 inhibits tumor growth [161]. In addition to tumor cells, regulatory immune Treg cells [162] and M2 [163] macrophages express CD39 and CD73. Treg cells and M2 macrophages degrade ATP and produce adenosine via CD39 and CD73 to limit the proinflammatory effects of ATP and further lead to immunosuppression through the adenosine-A2AR or adenosine-A2BR signalling axis [162, 163]. In addition, published evidence showed that Treg cells inhibited the antitumor activity of NK cells to promote the metastasis of melanoma in a CD39-dependent pathway in mice [161]. Notably, the activities of A2AR and A2BR effectively promote immunosuppression in inflammatory diseases [164]. It has been found that the activation of the

**TABLE 3** Clinical trials testing CD39 inhibitors and CD73 inhibitors in cancer therapy

ClinicalTrials.gov Identifier	Intervention/treatment	Condition or disease	Phase
NCT04262375	Durvalumab (PD-L1 inhibitor) Oleclumab (CD73 inhibitor)	Non-small Cell Lung Cancer Renal Cell Carcinoma	II
NCT03773666	Durvalumab (PD-L1 inhibitor) Oleclumab (CD73 inhibitor)	Muscle Invasive Bladder Cancer	I
NCT03616886	Paclitaxel Carboplatin MEDI4736 (PD-L1 inhibitor) MEDI9447 (CD73 inhibitor)	Triple Negative Breast Cancer	I/II
NCT03822351	Durvalumab (PD-L1 inhibitor) Oleclumab (CD73 inhibitor) Monalizumab (NKG2A inhibitor)	Stage III Non-small Cell Lung Cancer Unresectable	II
NCT03884556	TTX-030 (CD39 inhibitor) Pembrolizumab (PD-1 inhibitor) Docetaxel Gemcitabine Nab-paclitaxel	Solid Tumor Lymphoma	I
NCT03381274	MEDI9447 (CD73 inhibitor) Osimertinib (EGFR inhibitor) AZD4635 (A2AR inhibitor)	Non-small Cell Lung Cancer	I/II
NCT04089553	AZD4635 (A2AR inhibitor) Oleclumab (CD73 inhibitor) Durvalumab (PD-L1 inhibitor)	Prostate Cancer Metastatic Castration-Resistant Prostate Cancer	II
NCT04261075	IPH5201 (CD39 inhibitor) Durvalumab (PD-L1 inhibitor) Oleclumab (CD73 inhibitor)	Advanced Solid Tumors	I

Abbreviations: A2AR: A2a receptor; EGFR: epidermal growth factor receptor; NKG2A: NK group 2 member A; PD-1: programmed death 1; PD-L1: programmed cell death-ligand 1.

adenosine-A2AR signalling axis promoted the expression of PD-1 [165] and inhibited the expression of the IL-2 receptor and proliferation after TCR stimulation of tumor-infiltrating T cells [166], which thereby inhibited antitumor immune function. Moreover, activation of the adenosine-A2AR signalling axis promoted the recruitment of MDSCs and the expression of vascular endothelial growth factor (VEGF) in tumors of mouse models [167], and these effects promoted tolerogenic DCs to express PD-L2 and IL-10 to inactivate Teff cells [168]. Consistently, PSB1115, an inhibitor of A2BR, inhibits tumor angiogenesis and promotes the accumulation of T cells in the TME [167].

Therefore, targeting ATP/adenosine metabolism is an effective strategy to relieve immunosuppression. Specifically, CD39 deletion has been found to lead to defects in angiogenesis and melanoma cell migration, which inhibits tumor progression in a mouse model [169]. Adenosine 5'-( $\alpha,\beta$ -methylene)diphosphate, a specific CD73 inhibitor, prevented breast cancer cell migration by affecting adenosine production [170]. Moreover, some lines of evidence indicated that both CD73 inhibitors [165] and A2AR antagonists [171] synergized with ICIs to inhibit

tumor progression in mouse models. Drugs targeting the adenosine signalling pathway combined with ICIs in cancer patients are currently in clinical trials. CPI-144, an A2AR inhibitor, has been demonstrated to be effective in controlling refractory renal cell carcinoma (RCC; disease control rate of 60%) and can further significantly improve the control effect when combined with atezolizumab (anti-PD-L1 antibody; disease control rate of 100%) in a phase I/Ib trial (NCT02655822) [172]. A list of clinical trials testing CD39 and CD73 inhibitors are shown in Table 3.

## 2.5 | Hypoxia

Hypoxia is a common feature of the TME caused by rapid cancer cell proliferation and an abnormal tumor vasculature [173]. Hypoxia is sensed by the O<sub>2</sub>/prolyl hydroxylase/Von Hippel Lindau axis, which stabilizes and activates HIF-1 and contributes to the immunosuppressive microenvironment [173]. HIF-1 shifts metabolism from OXPHOS to aerobic glycolysis by activating the expression of glucose transporter, which is necessary for cells to increase their glucose uptake and glycolysis,

and the expression of genes encoding glycolytic enzymes and lactate dehydrogenase [174]. Recent evidence showed that lncRNA calcium-dependent kinase activation activated the nuclear factor kappa-B (NF- $\kappa$ B) pathway and induced tumor microenvironment remodeling under hypoxic tumor conditions [175, 176]. In addition, HIF-1 increases extracellular adenosine production and accumulation by inducing CD39 and CD73 [157] and inhibiting ENT [158]. HIF-1 also promotes tumor progression via other pathways, including cell immortalization, stem cell maintenance, genetic instability, and chemotherapy resistance, by directly or indirectly regulating the transcription of multiple target genes [177]. Although the stability of HIF-1 $\alpha$  enhances the function of cytotoxic T cells, T cell activation is inhibited under hypoxic conditions, and this effect is enhanced under glucose-limited conditions [178]. Increasing lines of evidence show that glycolytic tumor mitochondrial metabolism plays a role in immunosuppression [179]. The available evidence showed that TILs in the TME derived from cancer cells with stronger OXPHOS exhibited reduced IFN- $\gamma$  secretion and cytolytic activity, whereas OXPHOS-deficient tumors showed less hypoxia and more functional TIL activity. In addition, OXPHOS-deficient tumors were more responsive to anti-PD-1 therapy, which highlighted the effect of OXPHOS-mediated hypoxia on TIL function and ICI efficacy [180]. Therefore, hypoxia/HIF-1 is a promising therapeutic target. The exposure of a mouse model to respiratory hyperoxia resulted in reduced hypoxia, increased T cell infiltration, and a stronger antitumor response in the tumor, which indicated that hypoxia played a crucial role in suppressing the antitumor immune response. Several HIF inhibitors have been found to have antitumor activities. The first class of drugs is cardiac glycosides, which inhibit HIF-1 $\alpha$  synthesis [181]. The second class of drugs is anthracycline chemotherapy drugs, including daunorubicin and doxorubicin, and these drugs impair the DNA-binding activity of HIF-1 [182]. The third class of drugs includes acriflavine, which blocks HIF-dependent gene transcription by binding to the PAS-B subregions of HIF-1 $\alpha$  and HIF-2 $\alpha$  [183]. However, the results of clinical trials with HIF-1 inhibitors are not ideal [184] due in part to the complex signal network and overlapping mechanisms mediated by HIF-1 in tumor cells and immune cells in the TME.

In addition, HIF-1 and TME acidification drive the expression of VEGF to activate VEGF-R, which triggers angiogenesis and vascular aberrations. Vascular aberrations in the TME lead to nutritional deficiency and damage the infiltration of lymphocytes into tumors, which leads to tumor immune escape [185]. In addition to inducing vascular malformations, VEGF is also directly involved in inhibiting antitumor immune responses [186]. VEGF

inhibits the maturation of DCs, which leads to the inactivation of CTLs [187]. Some evidence showed that VEGF significantly reduced the cytotoxic activity of T cells extracted from peripheral blood samples, and anti-VEGFR2 reversed the suppression of T cells caused by VEGF [188]. VEGF also promotes the immunosuppressive TME by inducing Tregs, TAMs, and MDSCs [189]. Consistently, the published evidence demonstrated that vessel normalization contributed to the efficacy of immunotherapy by promoting the delivery of ICIs and improving lymphocyte infiltration. This approach might provide an effective strategy for the treatment of tumors. Several clinical trials have been conducted for multiple tumor types and with different environments to evaluate the combination of anti-PD-L1, anti-PD-1, or anti-CTLA-4 and anti-VEGF therapies (Table 4).

## 2.6 | Ionic environment

Extracellular ions in the TME determine the immune response. Tumors often contain necrotic regions due to nutritional deficiencies. A recent study found a markedly higher concentration of potassium ions (K<sup>+</sup>) in tumor interstitial fluid compared with that in serum, which could inhibit CD8<sup>+</sup> T effector function through suppression of AKT-mTOR signalling. CD8<sup>+</sup> T effector function could be restored by decreasing intracellular [K<sup>+</sup>] in CD8<sup>+</sup> T cells, either pharmacologically or through the overexpression of a K<sup>+</sup> efflux channel [190]. Abnormal accumulation of K<sup>+</sup> in the TME contributes to impaired T cell effector function without inhibiting T cell proliferative potential. Mechanistically, a high concentration of extracellular K<sup>+</sup> limits nutrient absorption by T effector cells and induces a starvation response, which is characterized by increased autophagy, upregulated mitochondrial metabolic activity, and decreased histone acetylation, and these effects lead to the inhibition of effector functions [191]. Intriguingly, although the activity of T cells is inhibited at high potassium concentrations, adoptively transferred CD8<sup>+</sup> T cells activated in the presence of high potassium levels exhibit improvements in their durability, antitumor activity, and pluripotency due to metabolic reprogramming caused by the starvation response [191]. Thus, potassium induces T cell metabolic reprogramming in the TME, which further results in improved antitumor immune responses.

## 3 | ROLE OF MICROBIAL METABOLITES IN CANCER IMMUNITY

Because the intestinal flora is a key component of digestion, food residues and the compounds produced by the host and microorganisms are fermented by the

**TABLE 4** Clinical trials testing VEGF inhibitors in cancer therapy

ClinicalTrials.gov Identifier	Intervention/treatment	Condition or disease	Phase
NCT00790010	Bevacizumab (VEGF inhibitor) Ipilimumab (CTLA-4 inhibitor)	Melanoma	I
NCT01633970	5-FU Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor) Carboplatin Leucovorin Nab-paclitaxel Oxaliplatin Paclitaxel Pemetrexed	Advanced Solid Tumors	I
NCT01984242	Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor) Sunitinib (VEGFR inhibitor)	Renal Cell Carcinoma	II
NCT02039674	Pembrolizumab (PD-1 inhibitor) Paclitaxel Carboplatin Bevacizumab (VEGF inhibitor) Pemetrexed Ipilimumab (CTLA-4 inhibitor) Erlotinib (EGFR inhibitor) Gefitinib (EGFR inhibitor)	Non-small Cell Lung Carcinoma	I/II
NCT02366143	Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor) Carboplatin Paclitaxel	Carcinoma Non-Small-Cell Lung Cancer	III
NCT02420821	Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor) Sunitinib (VEGFR inhibitor)	Renal Cell Carcinoma	III
NCT03434379	Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor) Sorafenib (VEGFR inhibitor)	Carcinoma Hepatocellular	III
NCT03596281	Pembrolizumab (PD-1 inhibitor) Bevacizumab (VEGF inhibitor) Pegylated liposomal doxorubicin	Ovarian Cancer	I
NCT03847428	Durvalumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor)	Hepatocellular Carcinoma	III
NCT04091217	Atezolizumab (PD-L1 inhibitor) Bevacizumab (VEGF inhibitor)	Melanoma	II

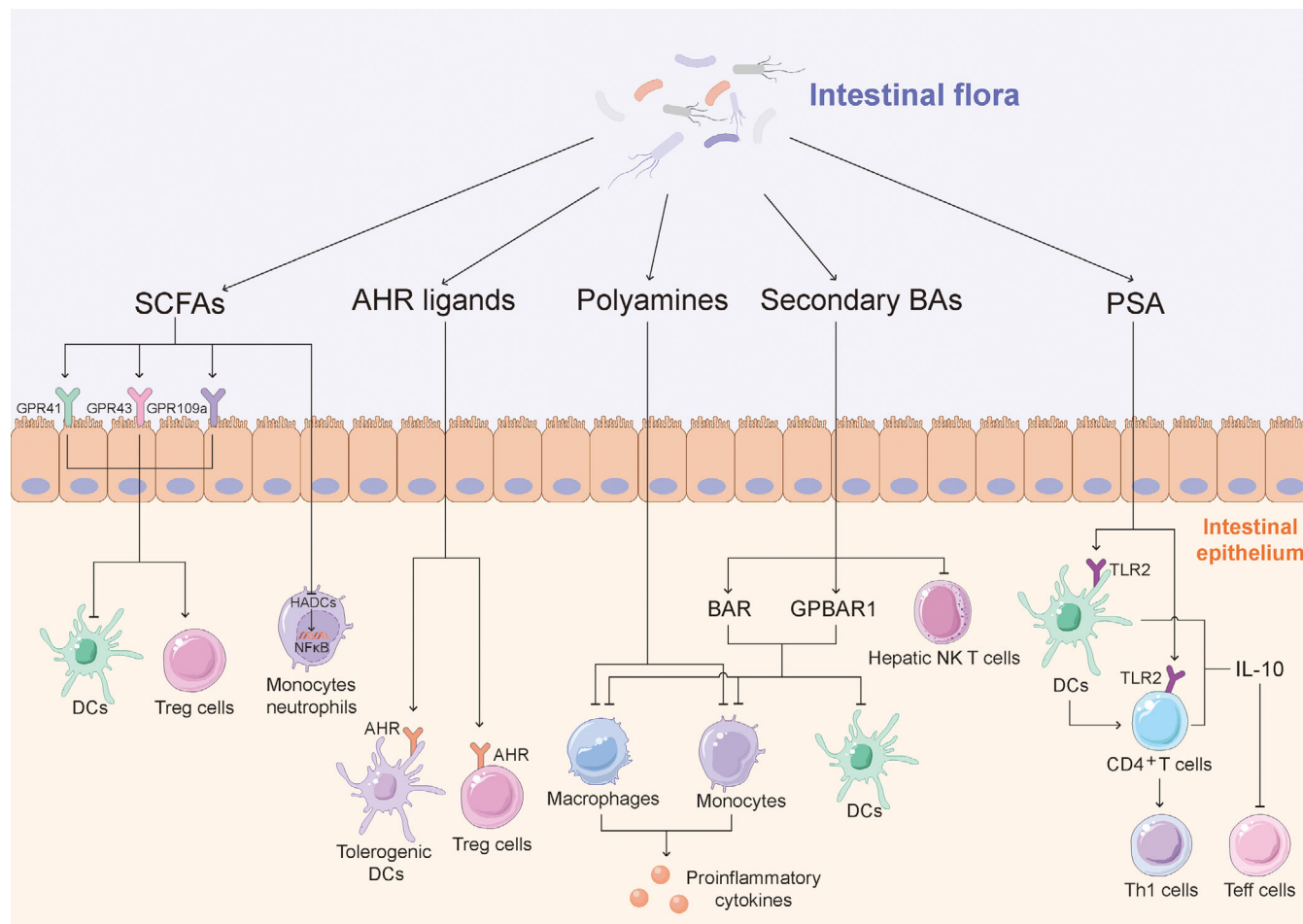
Abbreviations: CTLA-4: cytotoxic T lymphocyte-associated antigen-4; EGFR: epidermal growth factor receptor; PD-1: programmed death 1; PD-L1: programmed cell death-ligand 1; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

intestinal flora to generate abundant metabolites. Intestinal microbes and their metabolites further interact with host cells through intestinal epithelial monolayer cells, involving host immune activities and cancer progression. In addition, a link has been established between the microbiota composition and the immune checkpoint blockade efficacy in patients with melanoma [192, 193] or epithelial tumors [192, 193]. Moreover, the available data show that nearly half of the sources of plasma metabolites are closely related to bacteria, which indicates the crucial role of the microbiota in human metabolism [194]. Further-

more, bacterial metabolites, including short-chain fatty acids (SCFAs), AHR ligands, secondary bile acids (BAs), polyamines, and polysaccharides, might be involved in cancer progression and the efficacy of anticancer therapies by influencing the host immune system (Figure 4).

### 3.1 | SCFAs

SCFAs, primarily acetate, butyrate, and propionate, are products of the metabolism of polysaccharides and dietary



**FIGURE 4** Role of microbial metabolites in cancer immunity. SCFAs, AHR ligands, secondary BAs, polyamines and PSA, the bacterial metabolites, are involved in cancer progression and the efficacy of anticancer therapies by influencing the host immune system. SCFAs inactivate DCs and promote proliferation and immune regulation of Treg cells through GPR41, GPR43 and GPR109A, and inhibit the activity of NF- $\kappa$ B and the secretion of TNF in peripheral blood mononuclear cells and neutrophils by inhibiting HDAC. AHR ligands serve a function in regulating adaptive immunity through binding to AHR. BAs activate BAR and GPBAR1 to inactivate inflammation. In addition, secondary BAs, the products of primary BAs metabolized by bacteria, reduce hepatic NKT cells. PSA promotes CD4<sup>+</sup> T cells to express IL-10, induces naive CD4<sup>+</sup> T cell differentiation toward the Th1 subtype via a DC-dependent manner, and activates the expression of TLR2 to induce the secretion of IL-10, thereby inactivating Teff cells. Abbreviations: AHR: aryl hydrocarbon receptor; BAR: bile acids receptor; BAs: bile acids; DC: dendritic cell; GPBAR1: G protein-coupled BA receptor 1; GPR: G protein-coupled receptor; HDAC: histone deacetylase; IL: interleukin; NF- $\kappa$ B: nuclear factor kappa-B; NKT: natural killer T; PSA: polysaccharide A; Teff: effector T; TLR 2: Toll-like receptor 2; TNF: tumor necrosis factor; Treg: regulatory T; SCFA: short-chain fatty acid

fibre by *Clostridium* clusters IV and XIVa in the *Firmicutes* phylum, including species in the genera *Eubacterium*, *Roseburia*, *Faecalibacterium*, and *Coprococcus*, in the colon. Evidence showed that SCFAs, particularly propionate and butyrate, are involved in host immune activities. SCFAs activate the proliferation and function of immune cells by inhibiting histone deacetylase (HDAC) and activating G protein-coupled receptors (GPCRs). Because SCFAs are inhibitors of HDAC, SCFAs inhibit the activity of NF- $\kappa$ B and the secretion of TNF in peripheral blood mononuclear cells [195] and neutrophils [196]. Furthermore, the activities of macrophages and DCs are also inhibited by SCFAs [197, 198]. Thus, SCFAs are crucial for the regu-

lation of innate immunity. In addition to innate immunity, the HDAC inhibitory function of SCFAs acts on Treg cells to induce FOXP3 expression and thereby maintain intestinal homeostasis [199, 200]. In addition, animal models have revealed the immunoregulatory effect of HDAC inhibitors via Treg cells dependent on inflammatory diseases [201]. In addition to inhibiting HDAC, SCFAs regulate host immunity through GPCRs, including GPR41, GPR43, and GPR109A, which are expressed in a variety of cells, including intestinal epithelial cells and immune cells. The SCFA-induced activation of GPR41 inactivates DCs and improves the severity of allergic inflammation in a mouse model [198]. GPR43 stimulation induces



chemotaxis of neutrophils and promotes the proliferation and immune regulation of Treg cells [196, 202]. In a dextran sulphate sodium-induced and T cell transfer inflammatory bowel disease mouse model, SCFAs improve the severity of inflammation by recruiting and activating Treg cells in a GPR43-dependent manner [202, 203]. In addition, SCFAs promote the differentiation of Treg cells and IL-10-producing T cells, which results in the suppression of colitis and colon cancer in a GPR109a-dependent manner [204]. Taken together, the above-described findings demonstrate that SCFAs, the metabolites of microbes, are crucial to the regulation of inflammation and the prevention of tumorigenesis.

### 3.2 | AHR ligands

AHR ligands are a type of metabolite that binds to AHR to exert their function. AHR is a ligand-dependent transcription factor involved in the metabolism of exogenous compounds. Recent evidence has revealed the existence of endogenous AHR ligands [205]. As mentioned above, kynurenine, a catabolite of tryptophan, is an endogenous ligand of AHR, and evidence showed that kynurenine is induced by TDO and inhibits antitumor immune activity through the activation of AHR in both autocrine and paracrine forms [206]. Studies have suggested that AHR serves a function in regulating adaptive immunity and the differentiation of T cells and APCs [207, 208]. AHR participates in promoting the suppressive capacity of Treg cells by modulating DCs and also promotes the direct transactivation and induction of epigenetic modifications that control FOXP3 transcription [209]. The available evidence showed that AHR activation led to increased retinoic acid levels in DCs and deactivates signal transducer and activator of transcription 1 in T cells, which promoted the differentiation of Treg cells and suppressed Teff cells [209, 210]. Notably, the composition of the intestinal flora is an important factor in the activation of AHR. Specific bacterial subgroups, primarily *Lactobacillus*, can catabolize tryptophan to generate AHR ligands that activate AHR in innate lymphoid cells, which induces a balanced mucosal response that prevents colonization of the fungus *Candida albicans* [211]. Therefore, endogenous microbe-derived AHR ligands assist the host in preventing pathogen invasion and inflammation. Intriguingly, indole and 3-methyl indole, which are AHR ligands, exhibit species specificity for AHR activation, which indicates that ligands common to the microbiota and host have the potential for coevolution [212]. In summary, microbe-derived AHR ligands might play an important role in immunoregulation and immunopathology.

### 3.3 | Polyamines

Polyamines, the primary examples of which are putrescine, spermidine, and spermine, exist in all forms of organisms [213]. The synthesis of polyamines in mammals is gradually catalysed by ARG1, ornithine decarboxylase (ODC), and sequential enzymes that interconvert putrescine, spermidine, and spermine. Among these enzymes, ODC is the primary rate-limiting enzyme [213], and polyamines are produced by the intestinal flora via constitutive or inducible forms of amino acid decarboxylase, supporting the survival and toxicity of a variety of pathogens [214]. Polyamines are involved in key physiological processes that are crucial to host cells, such as gene transcription and translation, cell growth and death. Thus, the downregulation of ODC and polyamines leads to the suppression of cell growth, whereas the upregulation of polyamines promote tumorigenesis and tumor progression [213]. Polyamines also serve the function of regulating immunity. First, polyamines affect the function of innate immune cells. A high availability of polyamines inhibits the secretion of proinflammatory cytokines in macrophages and monocytes in response to LPS-stimulation. Spermine inactivates M1 macrophages by suppressing the expression of ODC and the production of proinflammatory cytokines without influencing the secretion of IL-10 or transforming growth factor- $\beta$  [215]. Consistently, treatment with polyamines improves the severity of localized and systemic inflammation in mice [216], and arginine in combination with probiotic *Bifidobacteria* LKM512 increases the level of polyamines, which in turn suppresses inflammation by decreasing TNF and IL-6 [217]. Accordingly, the colonic metabolic state might be improved by altering the dietary structure and through the appropriate intake of probiotics. Second, polyamines are involved in the modulation of adaptive immunity. Evidence showed that breast milk polyamines promoted the maturation of T cells, B cells, and NK cells in rats [218]. The role of polyamine metabolism in tumor progression was revealed in recent years. Similarly, a high availability of polyamines is needed to meet the fuel demands of tumor cells [213]. Samples from patients with intestinal cancer showed increased levels of polyamine metabolites, particularly N1- and N12-diacetylspermine, which are also associated with the mutual promotion of cancer cells and bacterial biofilms (BFs). Furthermore, antibiotic treatment could remove BFs and decrease the N1- and N12-diacetylspermine levels [219]. Thus, N1- and N12-diacetylspermine might represent BF-associated cancer biomarkers. In addition, evidence from a mouse model showed that polyamines were involved in suppression of antitumor immunity, and the depletion of polyamines activates Teff cells to limit tumor progression,

which indicated that reducing polyamines might represent a strategy for relieving immunosuppression in the TME [220]. In contrast, spermidine, one of the CR mimetics, induces autophagy and enhances the inhibitory effect of chemotherapy on tumor growth, and this effect depends on the depletion of Treg cells in the TME [80]. Similarly, a high spermidine intake is associated with an increased survival time in patients with cancer [221]. In addition to its metabolic function, spermidine act as a competitive inhibitor of acetyltransferase P300 to reduce the levels of acetyl-CoA and thereby induce autophagy [222, 223]. Notably, spermidine-induced autophagy is beneficial for anticancer immune surveillance [153]. Altogether, the abovementioned findings show that the regulatory mechanism of polyamines and the complex role of polyamines between microorganisms and hosts require further exploration.

### 3.4 | Bile acids

The synthesis of BAs occurs in the liver. Initially, cholesterol is oxidized by cytochrome P450 to generate primary BAs, which are conjugated to glycine or taurine to form bile salts before secretion. After being secreted into the intestinal tract, bile salts are further modified by intestinal bacteria into secondary BAs. Finally, approximately 95% of BAs are reabsorbed from the intestine and circulate to the liver via the portal vein [224]. Accordingly, the intestinal flora is crucial to the enterohepatic circulation of BAs. In addition to digestion, BAs have the function of regulating immune activities. First, BAs inhibit the secretion of proinflammatory cytokines from DCs, monocytes, macrophages, and Kupffer cells (resident macrophages in the liver) [225] via the bile acid receptor (BAR) and G protein-coupled BA receptor 1 (GPBAR1). In addition, both primary and secondary BAs can activate the two receptors [226]. BAR, a nuclear receptor, is a ligand-activated transcription factor that forms heterodimers with the retinoid X receptor. The activation of BAR in LPS-activated macrophages induces the transcription of BAR-dependent genes and inhibits the transcription of NF- $\kappa$ B-dependent genes through sumoylation-dependent stabilization of the nuclear receptor corepressor protein on the promoter, which results in the inhibition of proinflammatory cytokine expression [227]. Consistently, the inflammatory damage of colitis was alleviated in response to the administration of a BAR synthetic agonist [227, 228], but aggravated in BAR-deficient mice [227]. In addition to macrophages, hepatocytes and natural killer T (NKT) cells are also involved in the BAR deficiency-mediated activation of inflammation [229]. The activation of GPBAR1 by BAs contributes to increased intracellular cAMP levels, which acti-

vate extracellular signal-regulated kinases [230]. Similarly, synthetic agonists of GPBAR1 suppress the secretion of LPS-activated proinflammatory cytokines in macrophages and Kupffer cells by interfering with NF- $\kappa$ B-dependent transcription, and this effect is associated with direct inactivation of NF- $\kappa$ B and transcriptional competition between NF- $\kappa$ B and the cAMP-activated transcription factor cAMP response element-binding protein (CREB) [231]. Furthermore, the gut microbiota alter immune status through the metabolism of BAs. The expression of chemokine (C-X-C motif) ligand 16 (CXCL16), which inhibits tumor liver metastasis by inducing NKT cells, is increased by primary BAs but is decreased by secondary BAs in liver sinusoidal endothelial cells [232]. Moreover, vancomycin monotherapy leads to a reduction in Gram-positive *Clostridium* species, which play a central role in the production of secondary BAs, and thereby increase hepatic NKT cells. In addition, treatment with secondary BAs or colonization by *Clostridium scindens* leads to decreased hepatic NKT cells and increased liver metastases in vancomycin-treated mice [232]. Finally, 3-oxoLCA and isoalloLCA, metabolites of lithocholic acid, are involved in the regulation of T cells. The differentiation of Th17 cells is inhibited by the direct binding of 3-oxoLCA to the key transcription factor ROR $\gamma$ t, and the differentiation of Treg cells is promoted by isoalloLCA through the production of mitochondrial ROS [233]. Taken together, these data indicate that targeting the intestinal flora to regulate the metabolism of BAs might represent a promising strategy for cancer treatment through the regulation of immune cells.

### 3.5 | Polysaccharide

Zwitterionic polysaccharide A (PSA), which is produced by the common gut bacterium *Bacteroides fragilis*, is another microbial metabolite that serves as an immune modulator [234]. PSA promotes CD4+ T cells to express IL-10 and induces naive CD4+ T cell differentiation towards the Th1 subtype in a DC-dependent manner. Mechanistically, DCs stimulate the activation and clonal expansion of T cells by internalizing PSA and then presenting the antigen to CD4+ T cells [235]. In addition, TLR2 expression on the surface of DCs [236] and Treg cells [237] is activated by PSA to induce the secretion of IL-10, and PSA-induced IL-10 inactivates Teff cells, particularly Th17 cells, and thereby alleviates the symptoms of colitis in a mouse model [236]. Intriguingly, the immunosuppressive properties of PSA are essential for the intestinal colonization of *Bacteroides fragilis*, which indicates the mutualistic nature of the interactions between PSA and the immune system [237]. Moreover, the expression of CD39 on Treg cells is increased by PSA. Thus, PSA might be involved in

modulating ATP and adenosine signalling with systemic consequences [238].

### 3.6 | Intestinal flora and immunotherapy

Emerging knowledge on the ability of the gut microbiota to modulate the response to immunotherapy offers new possibilities to improve its efficacy by targeting the microbiota [192, 193, 239, 240]. CTLA-4 antagonists alter the composition of the intestinal flora and induce T cell-mediated mucosal damage in the ileum and colon. In general, treatment with CTLA-4 antagonists decreases both *Bacteroidales* and *Burkholderiales* (for example, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis* and *Burkholderia cepacia*) while increasing *Clostridiales* in a tumor-bearing mouse model [239]. The oral administration of either *B. thetaiotaomicron* or *B. fragilis* to microbiota-depleted mice restores the therapeutic response to anti-CTLA-4 by promoting the maturation of intratumoral DCs and inducing a Th1 response in the tumor-draining lymph nodes [239], which indicates that anti-CTLA-4 treatment might alter the composition of the gut microbiota in a direction that favours its antitumor activity in some patients. Similarly, the composition of the intestinal flora is also altered by PD-1/PD-L1 blockers to influence antitumor immunity. Moreover, the alpha diversity and relative abundance of bacteria in the *Ruminococcaceae* family are significantly higher in faecal microbiome samples from patients responding to checkpoint blockade immunotherapy. The results from an immune profile analysis showed that patients with a favourable gut microbiome, as well as germ-free mice receiving faecal transplants from responding patients, exhibited enhanced systemic and antitumor immunity [192]. In addition, a metagenomics analysis of patient stool samples obtained at diagnosis revealed that the abundance of *Akkermansia muciniphila* was most significantly associated with the clinical responses to ICIs. The oral administration of *Akkermansia muciniphila* after faecal microbiota transplantation with nonresponder faeces restores the efficacy of the PD-1 blockade by increasing the recruitment of CCR9+CXCR3+CD4+ T lymphocytes into mouse tumor beds [193]. Roberti et al. [241] also discovered that *B. fragilis* and *Erysipelotrichaceae* near ileal crypts induced DCs to activate the immune response of follicular helper T cells, which contributed to immunosurveillance against colon cancer and thus promotes the antitumor effects of chemotherapy and immunotherapy. Similarly, the administration of *Enterococcus hirae* containing a bacteriophage activates T cell responses after treatment with chemotherapy or immunotherapy [242]. The mechanism by which changes in the gut microbiota alters systemic immunity is under investigation, but a

recently published study by Tanoue et al. [243] showed that colonization of mice with a consortium of 11 bacterial strains from healthy human donors could improve CD8 T-cell-mediated immunity in several mouse models, and they demonstrated that the 11-strain consortium was associated with cecal and systemic elevation in metabolites, such as mevalonate and dimethylglycine, which might potentially augment immune function.

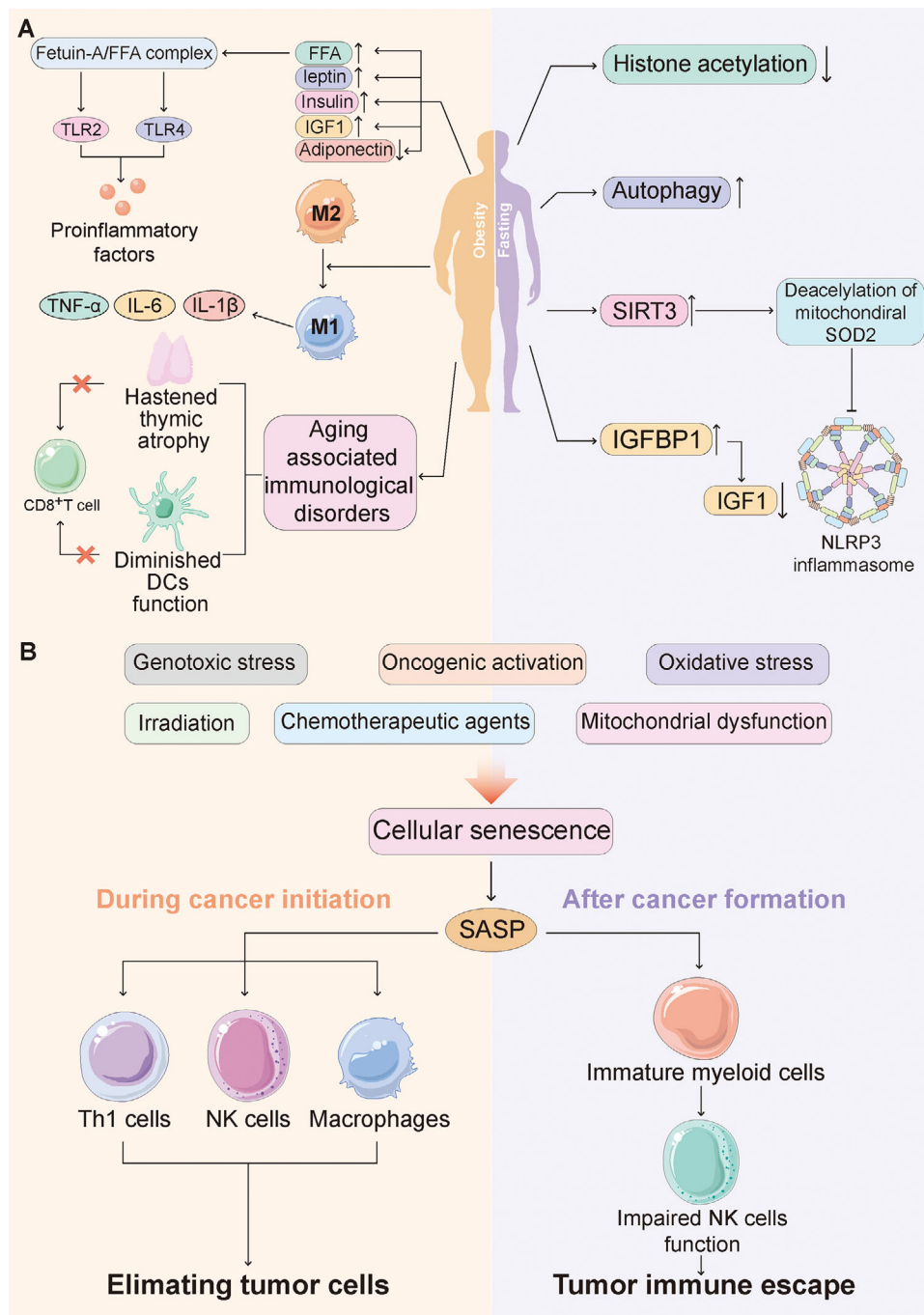
Based on the interaction between the microbiota and the host, the effect of using antibiotics to regulate the microbiome during cancer immunotherapy is complex. The oral administration of vancomycin improves the outcomes of cancer immunotherapy that targets CTLA-4 by depleting gram-positive *Clostridium* species [232]. Similarly, thiostrepton, an antibiotic produced by *Streptomyces azureus* and *Streptomyces laurentii*, synergizes with chemotherapy by enhancing anticancer immunogenicity [244]. However, antibiotics inhibit the effect of ICIs in advanced cancer [193], which indicates that the antibiotic-mediated effects might be context-dependent. Thus, natural antibiotics, which have narrow activity ranges, might be suitable for eliminating specific harmful microbial species. Evidence showed that the use of antianaerobic drugs, including carbapenem, cefmetazole, flomoxef, cefpirome, cefepime, clindamycin, and pazufloxacin, was associated with poor prognosis [245]. Accordingly, the targeted use of specific antibiotics and/or probiotics instead of the short-term or repeated use of broad-spectrum antibiotics to adjust the composition of the microbiome might be beneficial to tumor treatment efficacy.

## 4 | INFLUENCE OF SYSTEMIC METABOLISM ON REGULATION OF THE ANTITUMOR IMMUNE RESPONSE

The concept of “immunonutrition” has been developed due to awareness of the status of systemic nutritional influences on immune responses observed in epidemiological studies and clinical trials [246]. Nutritive variations, particularly obesity and fasting, exert immunomodulatory effects in the whole body. In addition, aging is characterized by generalized degeneration in a progressive manner, which leads to metabolic alterations and immunosuppression that drive tumorigenesis [247, 248] (Figure 5).

### 4.1 | Obesity

Obesity affects the occurrence and progression of a variety of cancers and is one of the most important avoidable causes of cancer [249]. A related link between obesity concurrent with metabolic syndrome and cancer has



**FIGURE 5** Influence of systemic metabolism on regulation of the antitumor immune response. (A) Obesity (left) is correlated with increased glucose, FFAs, leptin, insulin, and IGF1, along with decreased adiponectin, and induces the conversion of adipose-tissue macrophages from the M2 subtype to the M1 subtype, and is associated with aging-related immune dysfunctions. Relatively, fasting (right) induces histone acetylation, enhances autophagy, inactivates NLRP3 inflammasome, and decreases the bioavailability of IGF1. B. In response to various stimuli, cells undergo senescence and produce SASP, which is involved in eliminating incipient tumor cells during cancer initiation, while leading to immunosuppression after cancer formation. Abbreviations: IGF1: insulin-like growth factor 1; IGFBP1: insulin-like growth factor-binding protein-1; IL: interleukin; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; SIRT3: sirtuin 3; NK cell: NK: natural killer cell.; NLRP3: NLR family pyrin domain containing 3; SASP: senescence-associated secretory phenotype; SOD2: Superoxide dismutase 2; TLR 2: Toll-like receptor 2; FFAs: free fatty acids

been established. Metabolically, obesity is correlated with increased glucose, FFAs, leptin, insulin and insulin-like growth factor 1 (IGF1), decreased adiponectin, and an imbalance in the intestinal flora with a reduced barrier function, which contributes to endotoxemia and the overgrowth of bacterial species that produce carcinogenic metabolites [250, 251]. FFA induces TLR4 signalling in a fetuin-A-dependent manner, which culminates in increased activation of proinflammatory cytokines such as NF- $\kappa$ B and c-Jun N-terminal protein kinase 1 (JNK1) [252]. In addition, the conversion of adipose-tissue macrophages from the M2 subtype to the M1 subtype can be induced by obesity, and this conversion promotes the secretion of various proinflammatory cytokines, such as TNF, IL-6 and IL-1 $\beta$  [95, 253]. In addition, consistent with the theory that obesity is an inducer of aging [247], a variety of aging-related immune dysfunctions have been observed in individuals with obesity [254]. Specifically, the number and function of cells are inhibited, and the numbers of circulating V $\gamma$ 9+V $\delta$ 2+ T cells are reduced in these individuals [255]. These effects are accompanied by decreased levels of cytotoxic CD8+ T cells [256], which are properly induced by thymic atrophy [257] and the functional decline of DCs [258]. Evidence showed that the function of CD8+ T cells is impaired by high-fat diet-induced obesity through increases in the fat uptake of MC38 colorectal adenocarcinoma cells [259]. In addition, mammary adipose tissue macrophages enhance tumorigenesis of breast cancer by inducing stem-like properties in obese mice [181]. Obesity-related leptin reduction leads to increased PD-1 expression [260]. Consistently, some tumor immunotherapies are ineffective and even toxic in obese mice but show effectiveness in lean mice [261, 262]. The immunotherapy combination of  $\alpha$ CD40 and IL-2 induces a rapidly lethal cytokine storm in obese or aging mice caused by heightened production of TNF released from increased proinflammatory M1 macrophages [262]. These findings emphasize that obesity serves a function of promoting resistance to tumor immunotherapy.

Alleviating obesity is thought to be an effective strategy for preventing and treating cancer based on all the evidence relating obesity to a pro-tumor state both within the microenvironment and in peripheral circulation. Adjusting the diet and/or exercise to reduce weight restores multiple pathways that are dysfunctional under obese conditions and contributes to the prevention of tumor occurrence and progression. Several clinical studies have shown that significant calorie restriction and ketogenic or specific low-nutrient diets resulted in improvements in the subjective well-being, which indicates a reduction in side effects [263] and in inflammatory gene expression signatures within subcutaneous adipose tissues [264]. Patients with cancer who are overweight and obese could,

in theory, benefit from medications that stimulate weight loss. Finally, several medications, including metformin, everolimus and aspirin, could be beneficial in alleviating local and systemic inflammatory symptoms [265]. However, although preclinical data support the notion that metformin could enhance the effect of anti-PD-1 blockade [266], clinical trial data show that metformin can exert a synergistic effect to improve the curative effect of ICIs, but the effect was not statistically significant [267–269]. Although the website ClinicalTrials.gov provides information on multiple clinical trials that are either ongoing or completed, outcome information is generally lacking. It is worth investigating to see whether any of these studies have observed or will document a clinical benefit linked to a specific nutritional intervention.

In contrast, some recent data suggest an inverse relationship between body mass index and mortality in patients with cancer who receive immunotherapy [270–272]. The phenomenon might be explained by several reasons. Excess adipose tissue can serve as a potential energy reserve for cancer treatment, whereas malnutrition and cachexia might impair immune function [273]. In addition, the proinflammatory microenvironment in obesity might also be a reason. As mentioned above, although the inflammatory microenvironment caused by obesity is a recognized risk factor for tumorigenesis, this microenvironment also makes the level of immune cell infiltration in the TME significantly higher than that of patients with a normal weight. The immune cells in the TME are activated after immunotherapy, which results in a better prognosis in patients with obesity [270]. However, these concepts have not been verified experimentally, and no clinical trial has verified whether weight gain serves as an adjuvant treatment for malignant tumors. Taken together, the above-described findings indicate that obesity-overweight is a clear risk factor for tumorigenesis, but its association with cancer outcomes remains unclear. The pathophysiological mechanism underlying this process still needs to be further explored.

## 4.2 | Fasting

Fasting plays important roles in the metabolic response and immune function. Evidence showed that histone acetylation is reduced and autophagy is enhanced in leukocytes from both starved mice and human volunteers [274]. Similarly, caloric restriction exerts considerable anti-inflammatory effects and improves the function of immune cells [275]. Furthermore, a 24-hour fast can induce resistance to NLRP3 inflammasome activation by activating sirtuin 3 biology, and thereby reduces IL-1 $\beta$  secretion in human subjects [276]. In contrast, the coefficient

of bacterial products and glucose induces increases in the expression of macrophage-derived IL-1 $\beta$  in lean mice after feeding, which promotes the secretion of postprandial insulin [277]. Furthermore, some scholars have proposed that sickness-associated anorexia is an evolutionarily conserved reaction that regulates the immune response through the systemic upregulation of autophagic processes [278]. Moreover, caloric restriction mimetics (CRMs), a class of drugs or dietary supplements that reproduce the effects of CR, are reputed to promote health and even prolong the lifespan [279]. Evidence showed that starvation and multiple CRMs decrease the bioavailability of IGF1 by upregulating insulin-like growth factor-binding protein-1, which leads to large convergent metabolomic perturbations [80]. In addition, hydroxycitrate, a type of CRM, improves the effects of chemotherapy in a T cell-dependent manner [80]. Taken together, the findings indicate that CRMs appear to substantially facilitate immunosurveillance through systemic metabolic remodelling.

### 4.3 | Aging

Initially, cellular senescence was considered an irreversible exit from the cell cycle. However, senescence has since been identified as a stress response induced in response to various stimuli [280]. A number of studies have focused on aging-related metabolic characteristics [247] and further explored age-related biological changes through metabolomic characteristics [281]. The metabolic age score calculated by urine metabolomics can be used to evaluate the state of aging and predict survival and is independent of the chronological age and other risk factors [281]. Similarly, age-related characteristics and early pathological features of age-related diseases are reflected by serum metabolomics [282]. Recently, the relationship between longevity and the metabolic characteristics of different organs has been established by transspecies comparisons [283]. Moreover, the aging-induced accumulation of metabolites has been demonstrated to promote tumor progression and invasion [284].

Evidence indicates that longevity is positively correlated with sphingomyelin levels but negatively correlated with triacylglycerols containing polyunsaturated fatty acid (PUFA) side chains and by-products of inflammatory processes. PUFAs containing triacylglycerols have been consistently associated with shorter lifespans in human females [282]. In addition, naked mole rats, which have a life expectancy greater than 10 times that of rodents of the same size, have more polyamines and alpha-tocopherol (also known as vitamin E) in their plasma metabolites than do mice, and these metabolites have been shown to contribute to health and longevity in mice [285].

Longevity is negatively correlated with the hepatic levels of enzymatic cofactors that are involved in amino acid metabolism and the hepatic concentrations of tryptophan degradation products in several mammals. Therefore, the lifespan of animal models might be prolonged by reducing their intake of amino acids (particularly tryptophan and methionine), and daily weight-based caloric consumption might be one of the metabolic characteristics of long-lived mammals.

Importantly, the available evidence suggests that senescent cells can affect the TME. Ageing can cause immune dysfunction, which contributes to alterations in the TME during aging [286]. The senescence-associated secretory phenotype (SASP), the general term given to the combination of cytokines, chemokines, extracellular matrix proteases, growth factors, and other signalling molecules, is produced by senescent cells [287]. There are complex reciprocal interactions between the immune response and the SASP. The SASP is involved in recruiting immune cells to clear aging cells, which allows the SASP to recruit Th1 cells, NK cells, and macrophages to eliminate incipient tumor cells [288]. However, the SASP might also lead to immunosuppression. The coexistence of hepatocellular carcinoma (HCC) cells and premalignant senescent hepatocytes leads to the recruitment of immature myeloid cells by the SASP, which contributes to the impairment of NK cell function and thus promotes HCC [289]. Accordingly, there are multiple interactions among immune cells, senescent cells, and cancer cells.

## 5 | CONCLUSIONS AND PERSPECTIVES

In recent years, the field of cancer immunometabolism has attracted much attention [290, 291]. Studies on the metabolism of the TME have revealed the remarkable plasticity of cancer cells to obtain nutrients for growth and survival under the harshest conditions. In contrast, non-malignant cells are sensitive to nutrient consumption and metabolic waste accumulation. Specifically, both tumor cells and antitumor immune cells consume high amounts of glucose and glutamine, but tumor cells are more able to tolerate or even utilize lactate and hypoxia, which are harmful to antitumor immune cells and beneficial to immune regulatory cells. These differences provide opportunities for targeted metabolism. However, we need to be mindful of potential treatment toxicities because both tumor cells and immune cells often utilize the same metabolic pathways for proliferation. Some strategies might be applied to overcome this limitation. (A) One of these strategies involve developing new drug delivery methods that selectively modify specific immune cell subgroups or phenotypic metabolism. It is important to

consider that tumor cells and lymphocytes might differentially express amino acids and nutrient transporters, especially given the plethora of carriers involved in metabolism. The identification of metabolic targets that are selectively utilized in tumor cells might greatly improve antitumor immunity by avoiding detrimental effects on immune cells, and identifying these differences might allow the selective inhibition of metabolic pathways in cancer cells. (B) The second strategy combines metabolic intervention with chimeric antigen receptor T (CAR-T) cell therapy based on which manipulation of metabolic pathways can be precisely defined by genetic means. In addition, the metabolic characteristics of tumors that are responsive or nonresponsive to ICIs are different; thus, the relative utilization of glucose, amino acids, oxygen, or other nutrients might also be different. Therefore, studies aiming to determine the metabolic characteristics of ICI-resistant tumors might help identify targetable metabolic pathways in cancer cells that influence ICIs.

Caloric restriction promotes some anticancer therapies, and a high-fat diet might exacerbate malignant tumors. Similarly, calorie restriction can improve the incidence and severity of certain cancers. However, the operation of the diet will eventually regulate the intestinal microbiota, which, in turn, affects tumor and immune metabolism and even exerts a significant regulatory effect on various cancer types and immunotherapies. Although interference with the intestinal flora (directly through probiotics and/or faecal transplantation or indirectly through dietary changes) might be a promising strategy for individualized immunotherapy, caution should be taken because the impact of the diverse intestinal flora on the human body remains unclear.

At present, many topics in tumor immunonutrition remain to be improved, and these include the relationship between carcinogenic mutations and metabolic changes, which and how metabolic changes define the composition of the immunosuppressive TME, and whether the different metabolic characteristics of tumors of different types, stages and metastatic sites will affect multiple immune responses. Clarifying these issues will contribute to the development of personalised medicine for tumors. Further studies should include critically assessing the systemic changes in local metabolic phenotypes, whole body metabolism, and microbial communities.

#### DECLARATIONS

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

#### CONSENT FOR PUBLICATION

Not applicable.

#### AVAILABILITY OF DATA AND MATERIALS

Not applicable.

#### COMPETING INTERESTS

The authors declare that they have no competing interests.

#### AUTHORS' CONTRIBUTIONS

QW and SS performed and conceived the review. QW and XY wrote the manuscript. JL prepared all the figures. YT helped improved the quality of language and helped supply financial support. All the authors read and approved the final manuscript.

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