Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0645

REVIEW

Targeting tumor-infiltrating regulatory T cells based on immunometabolism

Na Li[1], Dexue Tian[2]

[1]Zhejiang Chinese Medical University, Hangzhou 310053, China; [2]Department of Breast Surgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China

ABSTRACT The immune checkpoint blockade (ICB) approach in cancer therapy involves the disruption of immune checkpoint inhibitory signals on tumor-specific CD8+ T cells, thereby reinstating the immune activity of CD8+ T cells and yielding therapeutic efficacy. However, due to the co-expression of immune checkpoint molecules, such as CTLA-4 and PD-1 on tumor-infiltrating Tregs (TI-Tregs) and conventional T cells (Tconvs), immune checkpoint inhibitors (ICIs) inadvertently amplify the immunosuppressive activity of Tregs while targeting CD8+ T cells, which contributes to the failure of immune therapy. Conventional strategies targeting Tregs, including ICI/conventional kinase and chemokine/chemokine receptor blockade, generally induce systemic Treg depletion, which triggers autoimmune diseases. Thus, achieving high selectivity and specificity in targeting TI-Tregs is of paramount importance in mitigating adverse immunologic reactions. Targeting metabolism-based TI-Tregs has been shown to enhance target precision, providing potential for the development of adjunctive immunotherapeutic strategies. This article explores the reciprocal interaction between TI-Tregs and the tumor microenvironment (TME), elucidating metabolic reprogramming, while envisioning plausible high-selectivity targets for TI-Tregs without compromising systemic immune homeostasis and immune reactivity of effector T cells.

KEYWORDS Tumor-infiltrating regulatory T cells; immunometabolism; immune checkpoint inhibitors; CD8+ T cells; tumor microenvironment

Introduction

Regulatory T cells (Tregs) are critical mediators in maintaining immune tolerance, achieving immune balance by suppressing inflammatory responses and excessive immune activation[1]. However, tumor-infiltrating regulatory T cells (TI-Tregs) function as accomplices to tumors within the tumor microenvironment (TME). Together, TI-Tregs and tumors suppress the cytotoxic activity of effector T cells against tumor cells, leading to functional exhaustion of effector T cells and facilitating tumor immune escape[2,3]. Furthermore, immune checkpoint blockade (ICB) therapy, which is achieved with anti-PD-1 antibodies, induces an increase in the number and immunosuppressive activity of Tregs in tumor tissues and the peripheral circulation[4]. This effect contributes to immune-related adverse events (irAEs) and tumor hyperprogression[5], complications that persist even in the context of neoadjuvant ICB therapy[6]. Studies have demonstrated that high Treg infiltration is associated with poorer immune prognosis in various malignancies[7]. Consequently, the abundance of Tregs within the TME and the frequency in the peripheral circulation can serve as immunologic predictors of tumor recurrence and metastasis[8]. Animal studies have shown that ICB therapy combined with Treg-targeting strategies can elicit potent anti-tumor immune responses[9], even activating systemic and sustained $CD8^+$ T cell-mediated anti-tumor immunity to suppress tumor recurrence and metastasis[6]. However, a critical drawback of targeting Tregs is the non-specific nature of current approaches. These therapies deplete Tregs not only in the tumor locale but also systemically, potentially causing severe autoimmune disorders and a profound disruption of immune homeostasis[10,11]. Therefore, identifying precise targets specific to TI-Tregs represents an effective pathway to prevent systemic Treg depletion. This strategy necessitates an in-depth investigation into the mechanisms allowing TI-Tregs to thrive and maintain potent immunosuppressive activity within the TME. Research must focus on how TI-Tregs remodel metabolic pathways in the metabolically challenging milieu characterized by hypoxia, and low glucose and high lactate levels. Building on these metabolic adaptations to discover highly specific TI-Treg targets is essential for overcoming the limitations of antibody-based cancer immunotherapies.

Correspondence to: Dexue Tian
E-mail: dexueT123@163.com
ORCID ID: https://orcid.org/0009-0005-3424-1931
Received October 22, 2025; accepted January 23, 2026.
Available at www.cancerbiomed.org
©2026 The Authors. Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Origin and classification of TI-Tregs

The abundant immunosuppressive Tregs within tumor tissues may originate from the following sources, which are generated in response to tumor antigens: peripheral Tregs (pTregs); thymus-derived Tregs (tTregs); and antigen-induced Tregs (iTregs)[12]. tTregs develop from $CD4^+$ T cell precursors in the thymus following stimulation by self-antigens presented by thymic epithelial cells. After maturation, tTregs migrate to peripheral tissues to maintain immune tolerance against self-antigens[13,14]. In contrast, pTregs differentiate from mature $CD4^+$ T cells in the periphery and have a decisive role in balancing immune responses to foreign antigens, while preventing autoimmunity[13]. iTregs often arise from naïve T cells within the TME that differentiate under the influence of local antigens and cytokines[15]. Tregs can be further categorized into central Tregs (cTregs) and effector Tregs (eTregs) based on immunosuppressive potency in human peripheral lymphoid and tumor tissues[16].

Three distinct subsets of Tregs have been identified, reflecting the phenotypic and functional heterogeneity[16]: ① $FoxP3^{lo}CD25^{lo}CD45RA^+$ Tregs, Fraction I (Fr. I) are quiescent, non-activated Tregs with minimal immunosuppressive activity. ② $FoxP3^{hi}CD25^{hi}CD45RA^-$ Tregs (Fr. II) differentiate into eTregs upon T cell receptor (TCR) stimulation by antigens in the periphery or TME. Activated eTregs exhibit enhanced proliferation and potent suppressive capacity and actively express surface molecules, including the activation marker, CD44, effector molecules, such as programmed cell death protein-1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and T cell immunoreceptor with Ig and ITIM domains (TIGIT)[17]. Concurrently, activated eTregs increase the secretion of immunosuppressive cytokines, like interleukin-10 (IL-10), interleukin-35 (IL-35), and transforming growth factor-beta (TGF-β)[12]. ③ $FoxP3^{lo}CD25^{lo}CD45RA^-$ Tregs lack significant immunosuppressive function and can secrete pro-inflammatory cytokines[16].

In summary, eTregs constitute < 5% of T cells in human peripheral blood but are highly enriched within the TME, where eTregs predominantly exert immunosuppressive effects[18].

Immunosuppressive mechanisms mediated by TI-Tregs

Tumor tissues facilitate the recruitment and enrichment of Tregs within the TME by releasing chemokines (e.g., CCL5 and CCL22) and cytokines (e.g., TGF-β and IL-10)[19], which interact with corresponding chemokine receptors (CKRs) on Tregs (e.g., CCR4, CCR8, CXCR4, and CXCR5)[20]. Tumor cells, through metabolic reprogramming, shape the TME into an immunosuppressive milieu characterized by hypoxia, and low glucose and high lactate levels[21]. This metabolic environment severely suppresses the cytotoxic activity of immune cells, particularly $CD8^+$ T cells[22]. In contrast, Tregs maintain robust immunosuppressive functions, even under these metabolically restrictive conditions[23]. What accounts for this stark functional difference between $CD8^+$ T cells and Tregs? Research indicates that the energy metabolism mechanisms within the TME are fundamentally distinct[24]. TI-Tregs exhibit metabolic flexibility, allowing TI-Tregs to adapt metabolic pathways, utilize tumor-derived metabolites, and thereby sustain immunosuppressive activity[25]. Furthermore, Tregs can actively suppress $CD8^+$ T cell activation and metabolism through metabolic interference (**Figure 1**)[26]. For example, Tregs hydrolyze extracellular ATP to adenosine, which then binds to the A2A receptor on $CD8^+$ T cells, inhibiting $CD8^+$ T cell activation[27]. In addition, CTLA-4 expressed on Tregs can induce indoleamine 2,3-dioxygenase (IDO) production in antigen-presenting cells (APCs). IDO catabolizes tryptophan into kynurenine, leading to tryptophan starvation and subsequent apoptosis of effector T cells (Teffs)[28].

In addition to metabolic suppression, Tregs employ multiple other mechanisms to impede Teff function, as follows (**Figure 1**): ① Tregs disrupt the APC-Teff signaling axis through distinct molecular checkpoints (e.g., PD-1, CTLA-4, LAG-3, and TIGIT)[29]. CTLA-4 mediates the trans-endocytosis of CD80/86, depriving Teffs of CD28 co-stimulation to induce anergy[30]. TIGIT competitively sequesters CD155, abrogating CD226 activation while eliciting APC-derived IL-10 *via* reverse signaling[31]. LAG-3 outcompetes CD4 for MHC-II binding to impose steric hindrance on TCR engagement. PD-1 ligates PD-L1 to reinforce Treg stability, while attenuating pro-inflammatory cytokine release from APCs[32]. ② Tregs secrete immunosuppressive cytokines (e.g., IL-10, IL-35, and TGF-β), inhibiting the proliferation and activation of Teffs and APCs. ③ Tregs directly eliminate Teffs *via* the perforin/granzyme B-dependent cytolytic pathway, a process strictly licensed by TCR signaling and high IL-2 availability. Mechanistically, this process involves the polarized exocytosis of cytotoxic granules into the immunologic synapse, where granzyme B triggers a caspase-dependent apoptotic cascade within the Teff[33]. ④ Tregs express the high-affinity CD25 receptor, IL-2Rα, competitively consuming IL-2, and thereby limiting IL-2 availability for Teffs[34].

In summary, Tregs exert potent immunosuppression by adaptively reprogramming metabolism within the TME and simultaneously disrupting the immunometabolism of $CD8^+$ T cells. Consequently, therapeutic strategies targeting these specific Treg immunosuppressive mechanisms are now being extensively explored.

Conventional strategies for targeting TI-Tregs

Limitations of targeting TI-Tregs in ICB therapy

Tregs express CTLA-4, which exhibits high affinity for CD80/86 on APCs. This CTLA-r expression enables Tregs to competitively inhibit binding between CD28 on conventional

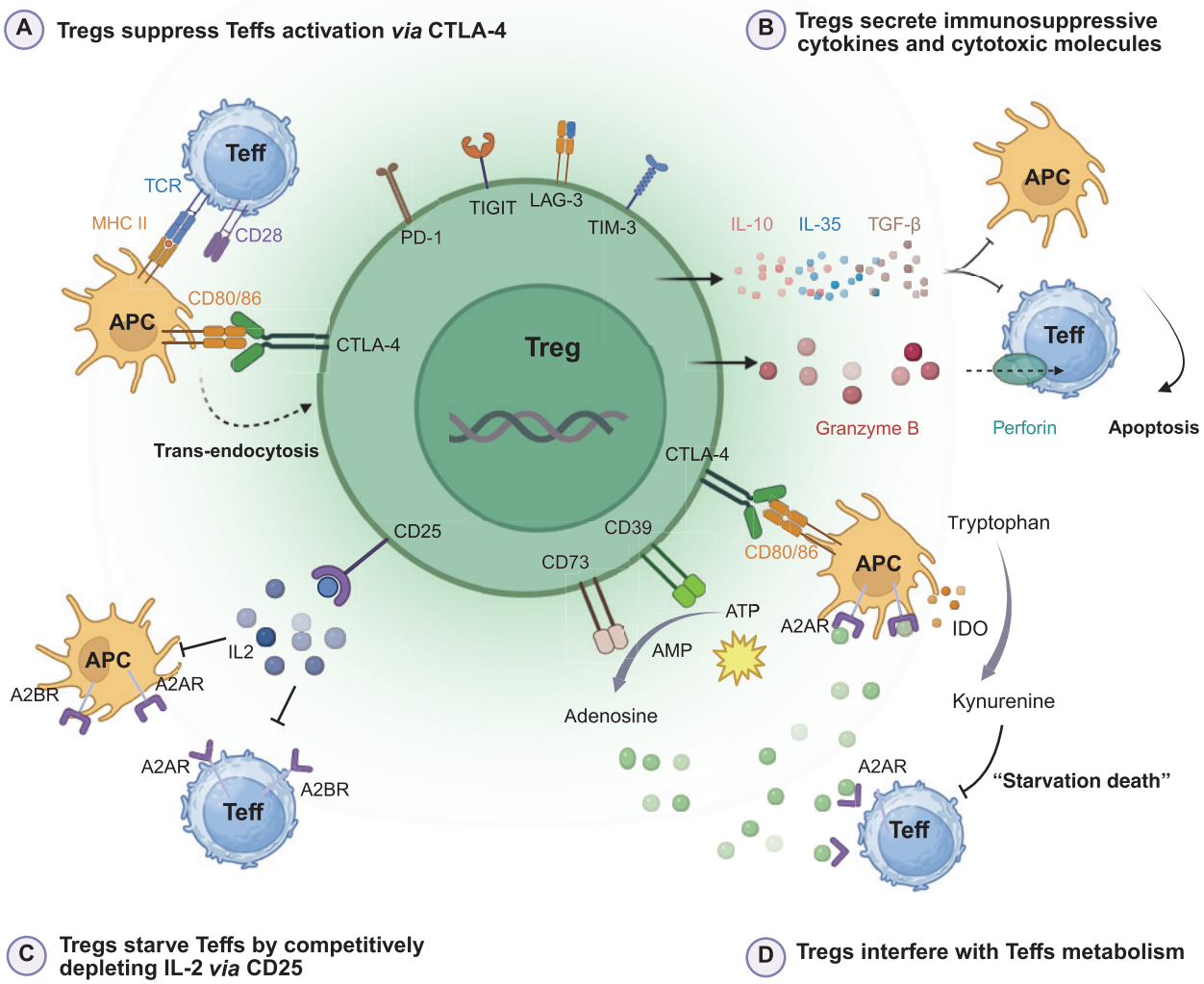


Figure 1 Representation of Treg-mediated suppressive mechanisms. (A) Tregs suppress Teff activation *via* CTLA-4. Tregs use CTLA-4 to competitively bind CD80/86 on APCs, resulting in depletion of the co-stimulatory molecules *via* trans-endocytosis into Tregs. (B) Tregs secrete immunosuppressive cytokines and cytotoxic molecules. Tregs suppress Teffs and APCs through secretion of immunosuppressive cytokines (IL-10, IL-35, and TGF-β) and induce apoptosis *via* cytotoxic molecules (granzyme B and perforin). (C) Tregs starve Teffs by competitively depleting IL-2 *via* CD25. Treg-mediated sequestration of IL-2 *via* the high-affinity CD25 receptor deprives Teffs of essential trophic signals, inducing apoptosis, while concurrently attenuating the cytokine-dependent activation of APCs. (D) Tregs interfere with Teff metabolism. Tregs convert extracellular ATP into adenosine *via* CD39 and CD73; the resulting adenosine interacts with A2A/A2B receptors on Teffs and APCs to inhibit activation. In addition, Tregs induce APCs to produce IDO *via* an interaction with CTLA-4. IDO converts tryptophan into kynurenine, resulting in the "starvation death" of Teffs. A2BR, adenosine A2B receptor; AMP, adenosine monophosphate; APC, antigen-presenting cell; ATP, adenosine triphosphate; CD25, cluster of differentiation 25; CD28, cluster of differentiation 28; CD39, cluster of differentiation 39; CD73, cluster of differentiation 73; CD80/86, cluster of differentiation 80/86; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IDO, indoleamine 2,3-dioxygenase; IL-2, interleukin-2; LAG-3, lymphocyte activation gene-3; MHC II, major histocompatibility complex class II; PD-1, programmed death-1; TCR, T cell receptor; Teff, effector T cell; TGF-β, transforming growth factor-beta; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin and mucin-domain containing-3. Created using BioRender.com.

T cells (Tconvs) and CD80/86, thereby impeding Tconv activation[35] and forcing Tconvs into an anergic state. PD-1 is highly expressed on Teffs and Tregs within the TME. PD-1 ligation serves to restrain the over-expansion of Tregs, while PD-1 ligation by PD-L1 drives Teff exhaustion and apoptosis by attenuating TCR signaling[36]. The high frequency of PD-1+ Tregs remains a hallmark of a potent immunosuppressive niche, although PD-1 signaling acts as a "brake" on Treg proliferation; blockade of this pathway can inadvertently lead to Treg hyper-activation[37].

Although current blockade therapies targeting CTLA-4 and PD-1 have demonstrated considerable efficacy in various malignancies[38], PD-1 blockade paradoxically activates PD-1$^+$ Tregs, thereby enhancing the immunosuppressive activity of TI-Tregs within tumors and contributing to treatment failure[36]. Furthermore, due to the lack of tumor tissue specificity in these targeting approaches, systemic Treg dysfunction is frequently induced. Studies utilizing CTLA-4 or PD-1 deficient mouse models have shown that most of the mice develop fatal autoimmune diseases due to Treg depletion[12]. Moreover, anti-CTLA-4 monotherapy has failed in several phase III or IV clinical trials and is associated with a higher incidence of irAEs compared to anti-PD-1/PD-L1 therapy[39]. The incidence of grade 3 and 4 irAEs can reach 90% in neoadjuvant settings by combining the anti-CTLA-4 antibody, ipilimumab, with the anti-PD-1 antibody, nivolumab, for melanoma patients[40].

While extensive preclinical evidence suggests that integrating ICB therapy with Treg-targeting strategies enhances efficacy in various tumor models[12], clinical translation remains challenging. Indeed, a substantial proportion of patients exhibit primary resistance to ICB and have a significant incidence of irAEs[41]. Specifically, dual CTLA-4/PD-1 blockade (e.g., ipilimumab + nivolumab) is associated with a markedly high grade 3–4 irAE incidence of approximately 59%[42]. Moreover, targeted systemic depletion of Tregs, such as *via* CCR4 (mogamulizumab) or CD25 (RG6292), often elicits severe autoimmune-like toxicities, including cutaneous reactions and gastrointestinal inflammation. These clinical observations underscore the profound risk of compromising peripheral immune tolerance when aggressively targeting the Treg compartment[43,44]. Consequently, the following critical challenge remains: how can the benefits of ICB therapy be extended to low- or non-responding patients without compromising safety through severe immune toxicities.

Exploratory research addressing TI-Treg targeting deficiencies

Genetic engineering of co-inhibitory receptors on TI-Tregs

To address the abovementioned therapeutic limitations, researchers developed HCAb4003-1, a fully human heavy-chain antibody (HCAb) comprising a CTLA-4-specific variable domain fused to an hIgG1 Fc region. This antibody exhibits high affinity for human CTLA-4 and effectively blocks the interaction with B7-1 (CD80) and B7-2 (CD86). Furthermore, owing to the compact molecular configuration and reduced molecular weight, HCAb4003-1 demonstrates superior tumor tissue penetration. In addition, due to the optimized Fc region, HCAb4003-1 exerts enhanced antibody-dependent cellular cytotoxicity (ADCC) in mouse models[45]. Further investigation is required to establish the safety and efficacy profile of HCAb4003-1, which is currently in preclinical development.

The CTLA-4-targeting monoclonal antibodies currently in clinical use, ipilimumab and tremelimumab, achieve relatively sustained efficacy primarily by enhancing Teff activity. However, induction of CTLA-4 lysosomal degradation in Tregs leads to systemic Treg depletion and frequent irAEs, which directly limit clinical utility[46]. To circumvent this issue, engineered antibodies, such as HL12 or HL32, have been designed. These antibodies dissociate from CTLA-4 after endocytosis, evade lysosomal degradation *via* an LRBA-dependent mechanism, and recycle back to the cell surface. This process helps maintain TI-Treg immunosuppressive function and reduces the incidence of autoimmune complications[47].

Genetic engineering efforts are also targeting other immunosuppressive molecules on Tregs, such as LAG-3, TIGIT, and TIM-3. Several resulting monoclonal antibodies are under ongoing investigation, with the long-term efficacy still being evaluated[48]. For example, IMP321, a chimeric recombinant fusion protein antibody targeting LAG-3, effectively stimulates dendritic cell proliferation, enhances antigen presentation by APCs, and mitigates Treg-mediated immunosuppression[49]. IMP321 has shown antitumor activity in patients with metastatic melanoma, metastatic breast cancer, and advanced renal cell carcinoma[50]. Other anti-LAG-3 antibodies, including BMS-986016, LAG525, and INCAGN02385, are currently undergoing clinical trials as monotherapies or in combination with anti-PD-1 antibodies. *In vitro* and *ex vivo* studies indicate that TIGIT targeting significantly reduces Treg frequency and TGF-β1 secretion, while also suppressing the immunosuppressive function of myeloid-derived suppressor cells. Several anti-TIGIT antibodies, such as BGB-A1217, COM902, and IBI939, remain under investigation[51]. Furthermore, the combination of anti-TIM-3 and anti-PD-L1 antibodies delayed tumor growth in a mouse model of head and neck squamous cell carcinoma. This combination enhanced effector T cell cytotoxicity, reduced Treg abundance, and improved survival, although the therapeutic effect was not sustained. Analysis of recurrent tumors revealed that the number of Tregs rebounded to pre-treatment levels[52].

Therefore, antibodies targeting co-inhibitory receptors on TI-Tregs remain an active area of exploration and development, yet the antibodies continue to be associated with varying degrees of irAEs[53].

Targeting tumor necrosis factor receptors (TNFRs) and CKRs to deplete TI-Tregs

In addition to targeting the immunosuppressive molecules on Tregs, alternative strategies focus on interfering with other key modulators of TI-Treg function within the TME. These modulators include specific TNFRs such as GITR, OX40, and CD27, as well as CKRs, like CCR4, CCR8, CCR5, CCR10, and CKR ligands (e.g., CCL20)[12].

TNFR2, encoded by the *TNFRSF1B* gene, is highly expressed on tumor cells and TI-Tregs[54]. Among Treg subsets, TNFR2+ Tregs exhibit the most potent immunosuppressive activity[55]. Mechanistically, TNFR2 signaling enhances the

NF-κB pathway to upregulate PD-L1 expression on tumor cells, which promotes immune escape[56]. TNFR2 signaling also induces mitochondrial hyperpolarization and ROS-mediated DNA damage in CD8+ T cells, leading to programmed death[57]. Consequently, targeting TNFR2 can selectively deplete TNFR2+ TI-Tregs and alleviate suppression of CD8+ T cells. Several TNFR2-targeting agents are currently under clinical evaluation. Monoclonal antibodies, such as BI-1808 and LBL-019, block TNFR2–TNF-α interaction, deplete TI-Tregs *via* FcγR-dependent mechanisms, and promote T cell activation and IFN-γ release[58,59]. Other agents, including SIM-235, inhibit Treg proliferation by suppressing NF-κB signaling[60]. In addition, bispecific approaches (e.g., BsADC and FT10-Fab) targeting TNFR2 and CCR8 have shown enhanced efficacy and sustained immune activation in preclinical models[61], particularly when combined with anti-PD-1 therapy[62]. Given the specific expression on TI-Tregs, TNFR2 represents a promising target for future cancer immunotherapy.

Research involving other TNF receptor superfamily members is also advancing. A study investigating the anti-GITR agonist, DTA-1, in hepatocellular carcinoma demonstrated the efficacy in reducing TI-Treg infiltration. However, DTA-1 failed to reactivate exhausted $CD8^+$ T cells and induced a shift in macrophage polarization from the M1-to-M2 phenotype[63]. This undesirable M2 polarization was effectively reversed when DTA-1 was combined with a Toll-like receptor 4 (TLR4) agonist[64]. Further research using *ex vivo* cultures of hepatocellular carcinoma tissue revealed that combining anti-GITR with anti-PD-1 therapy enhances the proliferative response of $CD4^+$ and $CD8^+$ tumor-infiltrating lymphocytes (TILs) to tumor antigens presented by mRNA-transfected autologous B-lymphoblastoid cells. These TILs exhibit significantly enhanced proliferation with increased secretion of IFN-γ and granzyme B upon stimulation with CD3/CD28 antibodies[65]. Researchers developed a bispecific IgG1 antibody, the human CTLA-4 × OX40 antibody (ATOR-1015), that was created by fusing the Ig-like V-type domain of human CD86 (a natural CTLA-4 ligand) to an agonistic OX40 antibody. ATOR-1015 was shown to induce T cell activation and Treg depletion *in vitro*. ATOR-1015 exhibited good tumor infiltration, reduced local TI-Treg abundance, and increased the number and activity of $CD8^+$ T cells in human OX40 transgenic mouse models. Furthermore, ATOR-1015 demonstrated significant TI-Treg-specific depletion and sustained $CD8^+$ T cell immunity across various syngeneic mouse models, including bladder, colon, and pancreatic cancers[66].

Mogamulizumab, a recombinant humanized monoclonal antibody developed for cutaneous T-cell lymphoma, has shown promising clinical efficacy. Mogamulizumab significantly reduced the levels of $CCR4^+$ T cells and $CCR4^+$ Tregs within the TME[67]. Blockade of the CCL3-CCR1/CCR5 and CXCL12-CXCR4 axes in an MLL-AF9-induced mouse model of acute myeloid leukemia (AML) inhibited the accumulation of TI-Tregs in the leukemic hematopoietic niche and delayed leukemia progression[68]. A clinical study involving FOLFOX-resistant colorectal cancer patients with high serum CCL20 levels showed that the chemotherapeutic agent, 5-FU, activates the FOXO1/CEBPB/NF-κB/CCL20 axis. This pathway subsequently recruits a large number of Tregs into tumor tissue, enhancing drug resistance. Consequently, the research team proposed the FOXO1/CEBPB/NF-κB/CCL20 axis as a potential therapeutic target for eliminating TI-Tregs[69].

In summary, while current strategies targeting TNFRs and CKRs have achieved desirable Treg depletion in some preclinical studies as monotherapies or in combination, the strategies often lack tumor site-specificity and require long-term preclinical observation. Most targeting antibodies are currently in the clinical trial phase.

Other potential targets for TI-Treg depletion

Although TI-Tregs can directly impair Teffs and APCs through immunosuppressive cytokines, such as IL-10, IL-35, and TGF-β[70,71], existing research indicates that IL-10 and IL-35 have crucial roles in modulating peripheral inflammation[71], while TGF-β is responsible for regulating the expression of Forkhead Box P3 (FoxP3) in Tregs[72]. Consequently, the feasibility of strategies targeting these immunosuppressive cytokines secreted by TI-Tregs requires careful evaluation.

The evidence summarized above demonstrates that conventional strategies for targeting TI-Tregs generally have poor specificity, often leading to systemic immune dysregulation[73]. Maintaining the delicate balance in the abundance and function of Teffs and Tregs is paramount for preventing autoimmune pathologies. Thus, a formidable challenge in developing TI-Treg-targeting strategies lies in achieving specific depletion of TI-Tregs without compromising the antitumor functions of Teffs, while minimizing the impact on peripheral Tregs.

An in-depth exploration of the TME has revealed that, malignant and immune cells typically undergo a rewiring of energy metabolism and biosynthetic pathways that is driven by environmental stress[74]. Just as metabolic reprogramming is a quintessential hallmark of cancer[21], TI-Tregs have evolved distinct adaptive metabolic pathways[75], a biological understanding that has been shaped by a series of foundational discoveries (**Figure 2**). Grounded in the emerging field of immunometabolism[76], this review delves into the metabolic reprogramming of TI-Tregs within the TME, postulates potential TI-Treg-specific therapeutic targets, and dissects the barriers impeding clinical translation.

Immunometabolism of TI-Tregs in the TME

Hypoxic microenvironment

The excessive proliferation of tumor cells and aberrant angiogenesis create a hypoxic TME, which activates hypoxia-inducible factor-1α (HIF-1α) within tumor tissues[77]. Most studies

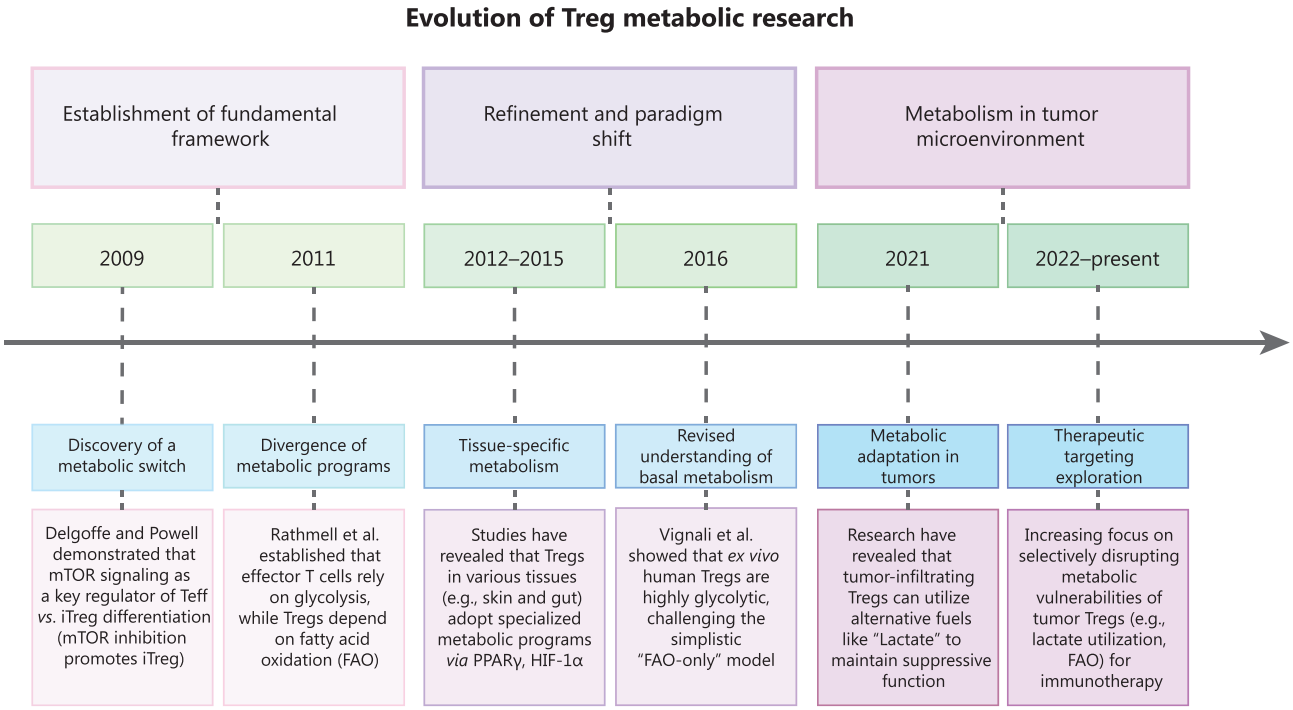


Figure 2 Evolution of Treg metabolic research. This timeline delineates key breakthroughs in regulatory T cell (Treg) metabolism, spanning from the initial characterization of the Treg lineage-to-the contemporary understanding of metabolic reprogramming within the tumor microenvironment (TME). Highlighted milestones include the discovery of FoxP3 as a master regulator, elucidation of nutrient-sensing pathways (e.g., mTOR and AMPK), and identification of distinct metabolic profiles, such as glycolysis and lipid metabolism, that govern Treg stability and suppressive function. Created using BioRender.com.

indicate that HIF-1α promotes the recruitment and migration of Tregs into the TME by stimulating vascular endothelial growth factor A (VEGF-A) production and/or enhancing the glycolytic rate in TI-Tregs[78]. Research utilizing an HIF-1α-deficient Treg mouse glioma model demonstrated reduced TI-Treg abundance in tumor tissues and improved mouse survival, suggesting that HIF-1α deficiency impairs Treg migration to tumor sites[79]. HIF-1α binds to Foxp3 protein *via* the N-terminal domain, recruiting PHDs and VHL to trigger Foxp3 ubiquitination and degradation. This binding abolishes Foxp3-mediated inhibition of the PI3K-Akt-mTOR axis, leading to glycolytic reprogramming and loss of suppressive activity in TI-Tregs[80] (**Figure 3**).

However, an alternative perspective suggests that HIF-1α can upregulate the expression of pyruvate dehydrogenase kinase 1 (PDK1) in TI-Tregs. This finding impedes the conversion of pyruvate to acetyl-CoA, inhibiting the tricarboxylic acid (TCA) cycle. Concurrently, HIF-1α upregulates various glycolytic enzymes, such as hexokinase (HK1/2), phosphofructokinase (PFKL/PFKP), phosphoglycerate kinase 1 (PGK1), and enolase (ENO1/2), promoting a metabolic shift towards glycolysis in TI-Tregs to facilitate adaptation to the hypoxic microenvironment[81] (**Figure 3**). Consequently, the precise mechanism by which HIF-1α influences TI-Treg function and metabolism remains controversial and warrants further investigation.

Lactate metabolism reprogramming

Tumor cells primarily rely on aerobic glycolysis, known as the Warburg effect, for glucose metabolism[82]. This process leads to substantial accumulation of lactate, which inhibits $CD8^+$ T and natural killer (NK) cell function[21,83]. In contrast, guided by the lineage-defining transcription factor, FoxP3, TI-Tregs primarily generate energy through oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO)[84]. In addition to promoting this specific energy metabolism profile in TI-Tregs[85], FoxP3 directly upregulates expression of the transmembrane glycoprotein, CD147, and monocarboxylate transporter 1 (MCT1) in eTregs, further mediating metabolic reprogramming in TI-Tregs[86] (**Figure 3**).

TI-Tregs import lactate *via* MCT1 and convert lactate into phosphoenolpyruvate (PEP). PEP subsequently supports OXPHOS, thereby promoting the proliferation and function of TI-Tregs within the TME[84] (**Figure 3**). Based on this finding, targeting PEP has been proposed as an immunometabolic strategy to disrupt ATP synthesis and inhibit TI-Treg proliferation[87]. Research indicates that MCT1 is essential for lactate

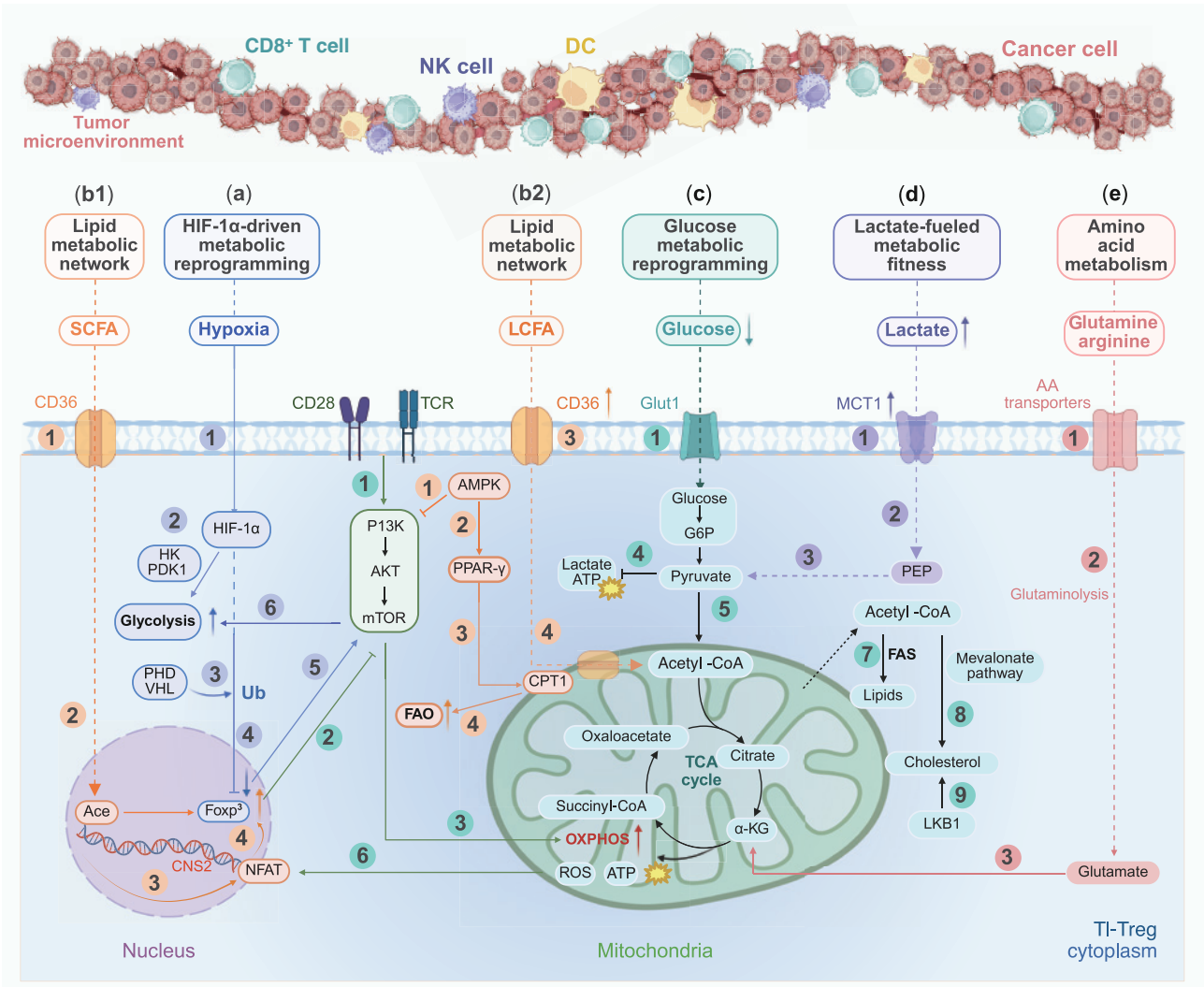


Figure 3 TI-Treg stability and function are governed by a complex metabolic network that balances nutrient utilization with lineage commitment. (a) HIF-1α-driven metabolic reprogramming. ① Hypoxia triggers the accumulation of HIF-1α, which exerts effects through dual regulatory mechanisms. ② First, HIF-1α directly upregulates transcription of glycolytic enzymes, such as HK1/2 and PDK1. ③ Second, HIF-1α facilitates recruitment of the PHD/VHL complex ④ to trigger Foxp3 ubiquitination and degradation. ⑤ This loss of Foxp3 relieves the constitutive inhibition of the PI3K-Akt-mTOR axis, ⑥ which consequently fuels enhanced glycolysis and impairs TI-Treg suppressive function. (b) Lipid metabolic network: TI-Tregs utilize CD36 to uptake environmental lipids, maintaining functional stability through two parallel metabolic circuits: (b1) SCFA signaling and (b2) LCFA signaling. (b1) SCFA signaling: ① TI-Tregs utilize CD36 to uptake SCFA. ② SCFA is processed into acetate (Ace). ① To drive LCFA utilization, the energy sensor, AMPK, represses the PI3K-Akt-mTOR axis to block competing glycolysis. ② Concurrently, AMPK activates PPAR-γ. ③ PPAR-γ subsequently coordinates upregulation of CD36 and CPT1 to boost lipid uptake and transport. ④ Finally, CPT1 promotes the mitochondrial entry of LCFAs for FAO and subsequent TCA cycle flux. (c) Glucose metabolic reprogramming. ① Co-stimulation *via* TCR and CD28 triggers Glut1-mediated glucose uptake and initiates PI3K-Akt-mTOR signaling. ② To tailor glucose utilization for Treg stability, Foxp3 suppresses PI3K-Akt-mTOR axis, ③ thereby shifting the metabolic program toward mitochondrial OXPHOS. ④ Consequently, pyruvate is diverted away from lactate production; ⑤ instead, pyruvate fuels the mitochondrial TCA cycle to generate ATP. ⑥ This mitochondrial respiration concurrently generates ROS, which drives NFAT activation to preserve TI-Treg stability. ⑦ Beyond energy production, mitochondrial acetyl-CoA is diverted into the FAS pathway for lipid synthesis. ⑧ Simultaneously, acetyl-CoA enters the mevalonate pathway to generate cholesterol, ⑨ a process regulated by LKB1. Collectively, these biosynthetic products support membrane lipid rafts and functional maturation, reinforcing TI-Treg immunosuppressive capacity. (d) Lactate-fueled metabolic fitness. ① TI-Tregs upregulate MCT1 to efficiently uptake tumor-derived lactate. ② Internalized lactate is processed into phosphoenolpyruvate (PEP), acting as a critical metabolic hub. ③ Subsequently, this lactate-derived PEP drives mitochondrial OXPHOS to generate ATP, thereby promoting the

proliferation and function of TI-Tregs within the TME. (e) Amino acid metabolism. ① TI-Tregs scavenge environmental arginine and glutamine *via* amino acid transporters. ② Internalized glutamine is converted into glutamate through glutaminolysis. ③ Subsequently, glutamate enters the TCA cycle to drive mitochondrial respiration. Collectively, this metabolic flexibility ensures TI-Treg persistence and robust immunosuppressive activity within the hostile tumor microenvironment. AA, amino acids; Ace, acetate; AKT, protein kinase B; AMPK, adenosine monophosphate (AMP)-activated protein kinase; α-KG, α-ketoglutarate; CCR, C-C chemokine receptor; CD28, cluster of differentiation 28; CD36, cluster of differentiation 36; CNS2, conserved non-coding sequence 2; CPT1, carnitine palmitoyltransferase-1; FAO, fatty acid oxidation; FAS, fatty acid synthesis; Foxp3, forkhead box P3; Glut1, glucose transporter 1; HIF-1α, hypoxia-inducible factor 1α; HK1/2, hexokinase 1/2; LC-FA, long-chain fatty acid; LKB1, liver kinase B1; MCT1, monocarboxylate transporter 1; mTORC, mammalian target of rapamycin complex; NFAT, nuclear factor of activated T cells; OXPHOS, oxidative phosphorylation; PDK, pyruvate dehydrogenase kinase; PEP, phosphoenolpyruvate; PHDs, prolyl hydroxylases; PI3K, phosphatidylinositol 3-kinase; PPAR-γ, peroxisome proliferator-activated receptor gamma; SC-FA, short-chain fatty acid; TCA, tricarboxylic acid cycle; TCR, T-cell receptor; TI-Treg, tumor-infiltrating regulatory T Cell; TME, tumor microenvironment; VHL, von Hippel-Lindau protein. Created using BioRender.com.

uptake and maintenance of strong immunosuppressive function in TI-Tregs, whereas MCT1 appears dispensable for Tregs from non-tumor sites[88]. Therefore, restrictive targeting of MCT1 within tumor tissues may represent a future approach to block lactate utilization by TI-Tregs.

TI-Tregs upregulate *Slc16a1* (encoding MCT1) and *Ldha* (a key lactate metabolism enzyme) under low or no glucose culture conditions, enhancing the capacity for lactate uptake and metabolism[88]. Consequently, targeting LDHA could theoretically inhibit lactate production by tumor cells *via* glycolysis, deprive TI-Tregs of a carbon source for OXPHOS, and alleviate the functional suppression of $CD8^+$ T cells in high-lactate environments. However, considering that pro-inflammatory cells in the TME, such as Teffs and M1 macrophages, also utilize glycolytic pathways as part of the metabolic reprogramming[89], an important question arises: would targeting LDHA also inadvertently suppress the glucose metabolism of these immune cells? Current evidence regarding this potential on-target, off-tumor effect is insufficient and requires further investigation. Similarly, the hypothesis of specifically targeting *Slc16a1* to precisely block lactate uptake in TI-Tregs remains to be validated through experimental studies.

Recent research has shown a positive correlation between lactate concentration in the TME and intracellular levels of PEP, Ga^{2+}, and nuclear factor of activated T-cells 1 (NFAT1) in TI-Tregs. Furthermore, NFAT1 promotes PD-1 expression on TI-Tregs. Based on these findings, some research groups have suggested considering lactate as a tumor-derived metabolic signal and a potential target for selectively targeting TI-Tregs[86].

Lactate metabolism and immunotherapy

Previous studies have indicated that PD-1 expression on eTregs in tumor tissues is associated with treatment resistance and hyper-progression during PD-1 blockade therapy[90]. Research in a mouse liver tumor model demonstrated that abundant lactate promotes PD-1 expression on TI-Tregs, leading to resistance against anti-PD-1 therapy. Genetic or pharmacologic inhibition of LDHA in tumor tissues or of MCT1 in TI-Tregs reduced intratumoral lactate levels, decreased PD-1 expression on TI-Tregs, and increased the abundance of activated $CD8^+$ T cells[86]. Therefore, targeting LDHA in tumors or MCT1 in TI-Tregs could, to some extent, overcome resistance to PD-1 blockade. Studies have shown that specific ablation of LDHA or MCT1 not only slows tumor growth but also synergizes with immune checkpoint blockade therapy[91].

Consequently, targeting MCT1 or LDHA to impair the metabolic fitness of TI-Tregs may yield the desired therapeutic effect. However, due to the distinct metabolic properties of tumors in different organs and inter-individual heterogeneity, the long-term efficacy and potential limitations of this strategy require continued validation and observation in animal models.

Glucose metabolism

FoxP3-mediated glucose metabolic reprogramming in TI-Tregs

FoxP3 serves as a key regulator mediating the metabolic reprogramming of TI-Tregs within the TME[92]. FoxP3 suppresses the phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-Akt-mTOR) signaling pathway, thereby reducing the glycolytic rate[24] (**Figure 3**). Analysis of microarray gene expression data has revealed that the presence of FoxP3 leads to strong downregulation of glycolytic and non-glycolytic *Myc* target genes[85]. Subsequent research further elucidated that FoxP3 reprograms TI-Treg metabolism by inhibiting *Myc* expression and glycolysis, while simultaneously enhancing oxidative phosphorylation and increasing oxidized nicotinamide adenine dinucleotide (NAD^+) levels[93]. FoxP3 profoundly influences the survival and functional state of TI-Tregs through transcriptional control over metabolic gene expression. Consequently, targeting FoxP3 may be considered a potential foundational strategy for eradication of TI-Tregs.

Research on glucose metabolism in TI-Tregs

TI-Tregs exhibit greater tolerance for high-lactate environments than high-glucose conditions. Elevated glucose levels in culture can impair TI-Treg function and stability because glucose uptake appears inversely correlated with the ability to maintain immunosuppressive function[88]. Glycolysis within the TME has a crucial role in the migration, proliferation, and immunosuppressive function of TI-Tregs[94,95], and this glycolytic process is subject to regulation by multiple factors.

The PI3K-Akt-mTOR pathway is a key hub regulating glycolysis. Enhancing PI3K-Akt-mTOR signaling can increase the glycolytic rate in TI-Tregs but paradoxically interferes with proliferation and stability[96,97]. Conversely, inhibiting the PI3K-Akt-mTORC1 signaling pathway reduces glycolysis while enhancing OXPHOS and FAO[98] (**Figure 3**). For example, using mTOR inhibitors to restrict glucose uptake and glycolysis in mouse B16-F10 melanoma models increased the number of TI-Tregs and strengthened the suppressive function[99,100]. PI3K-Akt-mTOR pathway activity is itself regulated by various upstream and downstream molecules, such as HIF-1α and AMP-activated protein kinase (AMPK)[101,102]. Studies have shown that metformin (an AMPK activator) suppresses mTOR activity and reduces glycolysis in TI-Tregs[103]. Inhibiting HIF-1α expression disrupts glycolysis and induces TI-Treg differentiation[104]. Using the hexokinase inhibitor, 2-deoxyglucose (2-DG), can promote TI-Treg proliferation[105].

The *Myc* gene is another important regulator of glycolysis; *Myc*-overexpressing tumors exhibit accelerated glycolytic rates[88]. While numerous studies have indicated that glucose uptake exerts an antagonistic effect on TI-Treg proliferation and function[106], recent research has confirmed that TI-Tregs can enhance mTOR activity to utilize glycolysis for meeting additional energy demands[107,108]. Alternatively, activation of the PI3K-Akt-mTORC1 pathway *via* TLR signaling increases Glut1-mediated glucose uptake and accelerates glycolysis in TI-Tregs, thereby promoting proliferation at the expense of suppressive function[24]. Furthermore, Tregs exhibit metabolic flexibility by utilizing different glucose metabolic pathways that depend on nutrient availability in normal versus metastatic tissues, effectively balancing glucose-lactate homeostasis.

The precise mechanisms through which glucose metabolism influences TI-Treg migration, proliferation, differentiation, and functional maintenance are incompletely understood and subject to considerable debate. Intervention strategies targeting TI-Treg glucose metabolism are still primarily in the clinical trial stage[4]. Specifically targeting TI-Treg glycolysis remains a promising yet prospective concept that requires more extensive investigation.

Fatty acid metabolism

Numerous studies have demonstrated that the proliferation of TI-Tregs primarily relies on FAO rather than glycolysis[84,109]. Both fatty acid synthesis (FAS) and FAO positively correlate with the suppressive function and stability of TI-Tregs[110,111] (**Figure 3**). Consequently, current strategies targeting TI-Treg lipid metabolism primarily focus on inhibiting FAS and FAO processes[112,113], such as modulating key enzymes and transporters involved in fatty acid metabolism. These strategies include AMP-activated protein kinase (AMPK), liver kinase B1 (LKB1), carnitine palmitoyltransferase 1 (CPT1), and the scavenger receptor, CD36[114,115].

Research has shown that pharmacologic inhibition of CPT1, a key rate-limiting enzyme in FAO, can suppress TI-Treg proliferation[116]. Similarly, targeting CD36 safely and effectively blocks lipid uptake specifically in TI-Tregs, inhibiting proliferation and differentiation within the tumor tissues without affecting systemic Treg populations[117]. Therefore, combining anti-CD36 therapy in mouse models with anti-PD-1 blockade has been shown to prevent the onset of autoimmune diseases[113].

Amino acid metabolism

Tryptophan and arginine are two essential amino acids involved in immune regulation. IDO, a rate-limiting enzyme, catabolizes tryptophan into kynurenine and 3-hydroxyanthranillic acid (3-HAA), subsequently promoting Treg proliferation *in vitro* and facilitating Treg migration into the TME[118] (**Figure 3**). The tryptophan metabolite, kynurenine, binds to the aryl hydrocarbon receptor, inducing tolerogenic dendritic cells (DCs) and promoting the generation and function of TI-Tregs[119]. Arginine deficiency impairs TI-Treg proliferation[120]. However, arginine can also stimulate IL-10 production by inducing DNA methylation in the IL-10 promoter region, consequently promoting TI-Treg generation[121]. Increased glutamate concentration within the TME promotes TI-Treg infiltration and weakens the anti-tumor immune response[122].

Thus, amino acid metabolism is crucial for the proliferation and differentiation of TI-Tregs. Although various IDO inhibitors have been developed, such as the secondary sulfonamide compound (Compound 5d), GDC-0919, INCB-024360, and NLG802, none have been approved for clinical use[123]. Therefore, a proposed strategy involves limiting the availability of amino acids essential for TI-Treg metabolism and inhibiting the production of their metabolites, thereby interfering with TI-Treg proliferation and effector functions.

In summary, TI-Tregs exploit metabolic intermediates in the TME *via* metabolic reprogramming, allowing for the flexible adaptation of macronutrient uptake and utilization (**Figure 3**). This metabolic flexibility is critical for proliferation, differentiation, and functional maintenance. Nevertheless, the precise mechanisms governing these processes remain a subject of debate and need to be better defined. While various therapeutic strategies targeting TI-Tregs have been postulated and investigated in preclinical and clinical trials (**Table 1**), highly

Table 1 Therapeutic strategies targeting Tregs in preclinical and clinical trials (partial list)

	Metabolic module	Target	Drug/compound	Metabolic mechanisms of Treg	Diseases and tumor types
Preclinical trials	Glucose metabolism	SKP2	SZL P1-41	Suppresses glycolysis and prevents Foxp3 degradation	Colitis/organ transplantation
	Mito dynamic	Drp1	Mdivi-1	Inhibits mitochondrial fission, halting Treg clonal expansion	T-Cell lymphoma/metastatic cancer
	Lipid metabolism	GPX4	RSL3/ML162	Induces ferroptosis in lipid-laden Tregs	Clear cell renal cell carcinoma/ melanoma
		FABP5	SBFI-26	Blocks lipid transport, destroying mitochondrial cristae integrity	Hepatocellular carcinoma/ colorectal cancer
		ACC1	TOFA	Blocks lipid synthesis, promoting Treg differentiation	Psoriasis/multiple sclerosis
		SREBP	Fatostatin	Stops *de novo* lipid synthesis	Ovarian cancer/refractory breast
	Lactate metabolism	MCT1	AZD3965	Blocks lactate uptake	Diffuse large B-cell lymphoma/ triple-negative breast cancer
	Amino acid metabolism	GCN2	GCN2iB	Disables adaptation to amino acid starvation in the TME	Melanoma/head and neck carcinoma
		ASCT2	V-9302	Blocks glutamine transport	Prostate cancer/lung cancer
		BCAT1	ERG240	Causes toxic BCAA buildup	Glioblastoma/hepatocellular carcinoma
	Epigenetics	HIF-1α	PX-478	Prevents metabolic adaptation to hypoxia, reducing Treg recruitment	Glioblastoma/pancreatic cancer
		ACL	BMS-303141	Targets ACLY to disrupt acetyl-CoA generation and Treg lipid metabolism	Lung cancer/breast cancer
Clinical trials	Glucose/Mito	Nrf2	Dimethyl Fumarate	Chemically modifies GAPDH to halt glycolysis, forcing T cells into a Treg-like metabolic state	Multiple sclerosis
		Complex I	Metformin	Inhibits respiration to reduce tumor hypoxia, decreasing the recruitment of Tregs	Lung/head & neck cancer
	Lipid metabolism	CD36	PLT012	Cut off fatty acid supply, starving Tregs that rely on OXPHOS	Advanced solid tumors
		HMGC-oA	Atorvastatin	Blocks geranylgeranylation needed to anchor CTLA-4 to the cell membrane	Breast cancer
	Adenosine pathway	CD73	Oleclumab	Halts adenosine production to unleash anti-tumor immunity	Lung cancer
		CD39	TTX-030	Inhibits CD39 to block adenosine production at the source	Pancreatic cancer
		A2AR	Ciforadenant	Blocks A2A receptors to prevent adenosine-driven Treg suppression.	Renal cell carcinoma
	Signaling hubs	CD38	Daratumumab	Inhibits CD38 to block NAD+ consumption and depletes Tregs	Non-small cell lung cancer
		IL-27	SRF388	Blocking IL-27-mediated TI-Treg induction and immunosuppression	Solid tumors

Table 1 Continued

Metabolic module	Target	Drug/compound	Metabolic mechanisms of Treg	Diseases and tumor types
	PI3Kδ	Idelalisib	Block AKT/mTOR signaling to downregulate Treg metabolism	Chronic lymphocytic leukemia
	IL-2R	Efavaleukin	Stimulates IL-2 signaling to enhance Treg metabolic fitness and expansion	Systemic lupus erythematosus
	mTORC1	Rapamycin	Inhibits mTORC1 to favor fatty acid oxidation, enhancing Treg stability	Amyotrophic lateral sclerosis/ transplant rejection
Modifiers	AhR	Tapinarof	Activates AhR to drive Treg differentiation and anti-inflammatory activity	Plaque psoriasis
	HPK1	NDI101150	Inhibits HPK1 to disrupt signaling homeostasis and induce Treg fragility	Advanced solid tumors

effective agents have yet to successfully transition into clinical practice. Consequently, considering the complex crosstalk within the TME, the identification of specific therapeutic targets on TI-Tregs requires continued exploration.

Conclusions

While ICB represents a paradigm shift in oncology, the clinical utility is frequently compromised by the paradoxical enhancement of Treg activity. Furthermore, systemic targeting of Tregs risks inducing severe autoimmunity, in which the resultant adverse events may negate clinical gains. Consequently, dissecting the specific metabolic adaptations of Tregs within the TME is essential for designing precision therapies against TI-Tregs. However, our current understanding of Treg metabolic adaptations within the TME remains limited. Specifically, the intricate metabolic-functional axis involving glycolysis and regulation of HIF-1α/FoxP3 expression warrants deeper exploration. Thus, the development of strategies for the precise and selective targeting of TI-Tregs continues to represent a significant challenge in the field.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Na Li.
Collected the data: Na Li.
Contributed data or analysis tools: Na Li, Dexue Tian.
Performed the analysis: Na Li, Dexue Tian.
Wrote the paper: Na Li.

References

1. Plitas G, Rudensky AY. Regulatory T cells in cancer. Annu Rev Cancer Biol. 2020; 4: 459-77.
2. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015; 15: 486-99.
3. Dikiy S, Rudensky AY. Principles of regulatory T cell function. Immunity. 2023; 56: 240-55.
4. Geels SN, Moshensky A, Sousa RS, Murat C, Bustos MA, Walker BL, et al. Interruption of the intratumor $CD8^+$ T cell: Treg crosstalk improves the efficacy of PD-1 immunotherapy. Cancer Cell. 2024; 42: 1051-66.e7.
5. Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, et al. Inhibitors of immune checkpoints—PD-1, PD-L1, CTLA-4—new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer Metastasis Rev. 2021; 40: 949-82.

6. Blomberg OS, Kos K, Spagnuolo L, Isaeva OI, Garner H, Wellenstein MD, et al. Neoadjuvant immune checkpoint blockade triggers persistent and systemic T_{reg} activation which blunts therapeutic efficacy against metastatic spread of breast tumors. Oncoimmunology. 2023; 12: 2201147.
7. Genova C, Dellepiane C, Carrega P, Sommariva S, Ferlazzo G, Pronzato P, et al. Therapeutic implications of tumor microenvironment in lung cancer: focus on immune checkpoint blockade. Front Immunol. 2022; 12: 799455.
8. Wu M, Huang Q, Xie Y, Wu X, Ma H, Zhang Y, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. J Hematol Oncol. 2022; 15: 24.
9. Marei HE, Hasan A, Pozzoli G, Cenciarelli C. Cancer immunotherapy with immune checkpoint inhibitors (ICIs): potential, mechanisms of resistance, and strategies for reinvigorating T cell responsiveness when resistance is acquired. Cancer Cell Int. 2023; 23: 64.
10. Dees S, Ganesan R, Singh S, Grewal IS. Regulatory T cell targeting in cancer: emerging strategies in immunotherapy. Eur J Immunol. 2021; 51: 280-91.
11. Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: can Treg cells be a new therapeutic target? Cancer Sci. 2019; 110: 2080-9.
12. Tay C, Tanaka A, Sakaguchi S. Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy. Cancer Cell. 2023; 41: 450-65.
13. Cinier J, Hubert M, Besson L, Di Roio A, Rodriguez C, Lombardi V, et al. Recruitment and expansion of tregs cells in the tumor environment—how to target them? Cancers (Basel). 2021; 13: 1850.
14. Koyama S, Nishikawa H. Mechanisms of regulatory T cell infiltration in tumors: implications for innovative immune precision therapies. J Immunother Cancer. 2021; 9: e002591.
15. Ohkura N, Sakaguchi S. Transcriptional and epigenetic basis of Treg cell development and function: its genetic anomalies or variations in autoimmune diseases. Cell Res. 2020; 30: 465-74.
16. Salvany-Celades M, van der Zwan A, Benner M, Setrajcic-Dragos V, Bougleux Gomes HA, Iyer V, et al. Three types of functional regulatory T cells control T cell responses at the human maternal-fetal interface. Cell Rep. 2019; 27: 2537-47.e5.
17. Ahmadzadeh M, Pasetto A, Jia L, Deniger DC, Stevanovic S, Robbins PF, et al. Tumor-infiltrating human $CD4^+$ regulatory T cells display a distinct TCR repertoire and exhibit tumor and neoantigen reactivity. Sci Immunol. 2019; 4: eaao4310.
18. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression—implications for anticancer therapy. Nat Rev Clin Oncol. 2019; 16: 356-71.
19. Shan F, Somasundaram A, Bruno TC, Workman CJ, Vignali DAA. Therapeutic targeting of regulatory T cells in cancer. Trends Cancer. 2022; 8: 944-61.
20. Iellem A, Mariani M, Lang R, Recalde H, Panina-Bordignon P, Sinigaglia F, et al. Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by $CD4^+$ $CD25^+$ regulatory T cells. J Exp Med. 2001; 194: 847-54.
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646-74.
22. Scharping NE, Menk AV, Moreci RS, Whetstone RD, Dadey RE, Watkins SC, et al. The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. Immunity. 2016; 45: 374-88.
23. Wang D, Quiros J, Mahuron K, Pai CC, Ranzani V, Young A, et al. Targeting EZH2 reprograms intratumoral regulatory T cells to enhance cancer immunity. Cell Rep. 2018; 23: 3262-74.
24. Gerriets VA, Kishton RJ, Johnson MO, Cohen S, Siska PJ, Nichols AG, et al. Foxp3 and Toll-like receptor signaling balance T_{reg} cell anabolic metabolism for suppression. Nat Immunol. 2016; 17: 1459-66.
25. Sasidharan Nair V, Saleh R, Toor SM, Cyprian FS, Elkord E. Metabolic reprogramming of T regulatory cells in the hypoxic tumor microenvironment. Cancer Immunol Immunother. 2021; 70: 2103-21.
26. Liu X, Hartman CL, Li L, Albert CJ, Si F, Gao A, et al. Reprogramming lipid metabolism prevents effector T cell senescence and enhances tumor immunotherapy. Sci Transl Med. 2021; 13: eaaz6314.
27. Shi L, Feng M, Du S, Wei X, Song H, Xu Y, et al. Adenosine generated by regulatory T cells induces $CD8^+$ T cell exhaustion in gastric cancer through A2aR pathway. Biomed Res Int. 2019; 2019: 4093214.
28. Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R, et al. Modulation of tryptophan catabolism by regulatory T cells. Nat Immunol. 2003; 4: 1206-12.
29. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018; 359: 1350-5.
30. Ding R, Yu X, Hu Z, Dong Y, Huang H, Zhang Y, et al. Lactate modulates RNA splicing to promote CTLA-4 expression in tumor-infiltrating regulatory T cells. Immunity. 2024; 57: 528-40.e6.
31. Cui H, Hamad M, Elkord E. TIGIT in cancer: from mechanism of action to promising immunotherapeutic strategies. Cell Death Dis. 2025; 16: 664.
32. Zhang A, Fan T, Liu Y, Yu G, Li C, Jiang Z. Regulatory T cells in immune checkpoint blockade antitumor therapy. Mol Cancer. 2024; 23: 251.
33. Imianowski CJ, Chen Q, Workman CJ, Vignali DAA. Regulatory T cells in the tumour microenvironment. Nat Rev Cancer. 2025; 25: 703-22.
34. Solomon I, Amann M, Goubier A, Arce Vargas F, Zervas D, Qing C, et al. CD25-T_{reg}-depleting antibodies preserving IL-2 signaling on effector T cells enhance effector activation and antitumor immunity. Nat Cancer. 2020; 1: 1153-66.
35. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. CTLA-4 control over Foxp3+ regulatory T cell function. Science. 2008; 322: 271-5.
36. Kumagai S, Togashi Y, Kamada T, Sugiyama E, Nishinakamura H, Takeuchi Y, et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. Nat Immunol. 2020; 21: 1346-58.
37. Lin X, Kang K, Chen P, Zeng Z, Li G, Xiong W, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers. Mol Cancer. 2024; 23: 108.

38. Sharma P, Goswami S, Raychaudhuri D, Siddiqui BA, Singh P, Nagarajan A, et al. Immune checkpoint therapy—current perspectives and future directions. Cell. 2023; 186: 1652-69.
39. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017; 377: 1824-35.
40. Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. Nat Rev Rheumatol. 2018; 14: 569-79.
41. Siddiqui MA, Usmani A, Ansari MN, Almoselhy RIM. Immune-related adverse events in immunotherapy: challenges in diagnosis, monitoring, and management. Toxicol Rep. 2025;14:102036.
42. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. J Clin Oncol. 2021; 39: 9506-6.
43. Zengarini C, Guglielmo A, Mussi M, Motta G, Agostinelli C, Sabattini E, et al. A narrative review of the state of the art of CCR4-based therapies in cutaneous T-cell lymphomas: focus on mogamulizumab and future treatments. Antibodies (Basel). 2024; 13: 32.
44. Gambardella V, Ong M, Rodriguez-Ruiz ME, Machiels JP, Sanmamed MF, Galvao V, et al. Safety and antitumor activity of a novel aCD25 Treg Depleter RG6292 as a single agent and in combination with atezolizumab in patients with solid tumors. Cancer Res Commun. 2025; 5: 422-32.
45. Gan X, Shan Q, Li H, Janssens R, Shen Y, He Y, et al. An anti-CTLA-4 heavy chain-only antibody with enhanced T_{reg} depletion shows excellent preclinical efficacy and safety profile. Proc Natl Acad Sci U S A. 2022; 119: e2200879119.
46. Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov. 2022; 21: 509-28.
47. Zhang Y, Du X, Liu M, Tang F, Zhang P, Ai C, et al. Hijacking antibody-induced CTLA-4 lysosomal degradation for safer and more effective cancer immunotherapy. Cell Res. 2019; 29: 609-27.
48. Li Q, Lu J, Li J, Zhang B, Wu Y, Ying T. Antibody-based cancer immunotherapy by targeting regulatory T cells. Front Oncol. 2023; 13: 1157345.
49. Aggarwal V, Workman CJ, Vignali DAA. LAG-3 as the third checkpoint inhibitor. Nat Immunol. 2023; 24: 1415-22.
50. Cai L, Li Y, Tan J, Xu L, Li Y. Targeting LAG-3, TIM-3, and TIGIT for cancer immunotherapy. J Hematol Oncol. 2023; 16: 101.
51. Chen BJ, Zhao JW, Zhang DH, Zheng AH, Wu GQ. Immunotherapy of cancer by targeting regulatory T cells. Int Immunopharmacol. 2022; 104: 108469.
52. Joller N, Anderson AC, Kuchroo VK. LAG-3, TIM-3, and TIGIT: distinct functions in immune regulation. Immunity. 2024; 57: 206-22.
53. Yang J, Bae H. Drug conjugates for targeting regulatory T cells in the tumor microenvironment: guided missiles for cancer treatment. Exp Mol Med. 2023; 55: 1996-2004.
54. Mohd Salim NH, Mussa A, Ahmed N, Ahmad S, Yean Yean C, Hassan R, et al. The immunosuppressive effect of TNFR2 expression in the colorectal cancer microenvironment. Biomedicines. 2023; 11: 173.
55. Chen X, Subleski JJ, Kopf H, Howard OM, Männel DN, Oppenheim JJ. Cutting edge: expression of TNFR2 defines a maximally suppressive subset of mouse $CD4^+CD25^+FoxP3^+$ T regulatory cells: applicability to tumor-infiltrating T regulatory cells. J Immunol. 2008; 180: 6467-71.
56. Luo S, Larson JH, Blazar BR, Abdi R, Bromberg JS. $Foxp3^+CD8^+$ regulatory T cells: bona fide Tregs with cytotoxic function. Trends Immunol. 2025; 46: 324-37.
57. Otano I, Alvarez M, Minute L, Ochoa MC, Migueliz I, Molina C, et al. Human CD8 T cells are susceptible to TNF-mediated activation-induced cell death. Theranostics. 2020; 10: 4481-9.
58. Mårtensson L, Cleary K, Semmrich M, Kovacek M, Holmkvist P, Svensson C, et al. Targeting TNFR2 for cancer immunotherapy: ligand blocking depletors versus receptor agonists. Cancer Res. 2020; 80: 936.
59. Nanjing Leads Biolabs Co., Ltd. Evaluation of LBL-019 monotherapy or combined with anti-PD-1 antibody in the treatment of advanced malignant tumors (ClinicalTrials.gov Identifier: NCT05223231); expected start date 2025. Available from: https://clinicaltrials.gov/study/NCT05223231.
60. Simcere. SIM0235, a TNFR2 monoclonal antibody independently developed by Simcere, received IND approval by the U.S. FDA in 2022. Available from: https://www.simcere.com/en/news/detail.aspx?mtt=208.
61. Li W, Li Q, Zhou Q, Wu Y, Wang MW, Ying T. A bispecific ADC against CCR8 and TNFR2 elicits potent antitumor efficacy. Med Drug Discov. 2025; 28: 100226.
62. Wang R, Xu J, Cheng S, Ling Z, Sonam W, Yang J, et al. TNFR2/CCR8 bispecific antibody enhances antitumor activity through depleting Ti-Tregs and boosting effector $CD8^+$ T cell function. Oncoimmunology. 2025; 14: 2497171.
63. Pedroza-Gonzalez A, Kwekkeboom J, Sprengers D. T-cell suppression mediated by regulatory T cells infiltrating hepatic tumors can be overcome by GITRL treatment. Oncoimmunology. 2013; 2: e22450.
64. Pan C, Wu Q, Wang S, Mei Z, Zhang L, Gao X, et al. Combination with toll-like receptor 4 (TLR4) agonist reverses GITR agonism mediated M2 polarization of macrophage in hepatocellular carcinoma. Oncoimmunology. 2022; 11: 2073010.
65. van Beek AA, Zhou G, Doukas M, Boor PPC, Noordam L, Mancham S, et al. GITR ligation enhances functionality of tumor-infiltrating T cells in hepatocellular carcinoma. Int J Cancer. 2019; 145: 1111-24.
66. Kvarnhammar AM, Veitonmäki N, Hägerbrand K, Dahlman A, Smith KE, Fritzell S, et al. The CTLA-4 x OX40 bispecific antibody ATOR-1015 induces anti-tumor effects through tumor-directed immune activation. J Immunother Cancer. 2019; 7: 103.
67. Ni X, Jorgensen JL, Goswami M, Challagundla P, Decker WK, Kim YH, et al. Reduction of regulatory T cells by Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients

with aggressive/refractory mycosis fungoides and Sezary syndrome. Clin Cancer Res. 2015; 21: 274-85.
68. Wang R, Feng W, Wang H, Wang L, Yang X, Yang F, et al. Blocking migration of regulatory T cells to leukemic hematopoietic microenvironment delays disease progression in mouse leukemia model. Cancer Lett. 2020; 469: 151-61.
69. Wang D, Yang L, Yu W, Wu Q, Lian J, Li F, et al. Colorectal cancer cell-derived CCL20 recruits regulatory T cells to promote chemoresistance via FOXO1/CEBPB/NF-κB signaling. J Immunother Cancer. 2019; 7: 215.
70. Moreau JM, Velegraki M, Bolyard C, Rosenblum MD, Li Z. Transforming growth factor-β1 in regulatory T cell biology. Sci Immunol. 2022; 7: eabi4613.
71. Sawant DV, Yano H, Chikina M, Zhang Q, Liao M, Liu C, et al. Adaptive plasticity of IL-10$^+$ and IL-35$^+$ T_{reg} cells cooperatively promotes tumor T cell exhaustion. Nat Immunol. 2019; 20: 724-35.
72. Yoshimura A, Muto G. TGF-β function in immune suppression. Curr Top Microbiol Immunol. 2011; 350: 127-147.
73. Li C, Jiang P, Wei S, Xu X, Wang J. Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. Mol Cancer. 2020; 19: 116.
74. Mathis D, Shoelson SE. Immunometabolism: an emerging frontier. Nat Rev Immunol. 2011; 11: 81.
75. Wang Y, Huang T, Gu J, Lu L. Targeting the metabolism of tumor-infiltrating regulatory T cells. Trends Immunol. 2023; 44: 598-612.
76. Artyomov MN, Van den Bossche J. Immunometabolism in the single-cell era. Cell Metab. 2020; 32: 710-25.
77. Sun J, Zhao Z, Lu J, An W, Zhang Y, Li W, et al. The tumor microenvironment mediates the HIF-1α/PD-L1 pathway to promote immune escape in colorectal cancer. Int J Mol Sci. 2024; 25: 3735.
78. Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene. 2010; 29: 625-34.
79. Miska J, Lee-Chang C, Rashidi A, Muroski ME, Chang AL, Lopez-Rosas A, et al. HIF-1α Is a metabolic switch between glycolytic-driven migration and oxidative phosphorylation-driven immunosuppression of tregs in glioblastoma. Cell Rep. 2022; 39: 110934.
80. Hsu TS, Lin YL, Wang YA, Mo ST, Chi PY, Lai ACY, et al. HIF-2α is indispensable for regulatory T cell function. Nat Commun. 2020; 11: 5005.
81. Wang Y, Li J, Nakahata S, Iha H. Complex role of regulatory T cells (Tregs) in the tumor microenvironment: their molecular mechanisms and bidirectional effects on cancer progression. Int J Mol Sci. 2024; 25: 7346.
82. Warburg O. On the origin of cancer cells. Science. 1956; 123: 309-14.
83. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, Russell S, Weber AM, Luddy K, et al. Neutralization of tumor acidity improves antitumor responses to immunotherapy. Cancer Res. 2016; 76: 1381-90.
84. Kempkes RWM, Joosten I, Koenen HJPM, He X. Metabolic pathways involved in regulatory T cell functionality. Front Immunol. 2019; 10: 2839.
85. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. Cell Metab. 2017; 25: 1282-93.e7.
86. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell. 2022; 40: 201-18.e9.
87. Ho PC, Bihuniak JD, Macintyre AN, Staron M, Liu X, Amezquita R, et al. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. Cell. 2015; 162: 1217-28.
88. Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature. 2021; 591: 645-51.
89. Hu C, Xuan Y, Zhang X, Liu Y, Yang S, Yang K. Immune cell metabolism and metabolic reprogramming. Mol Biol Rep. 2022; 49: 9783-95.
90. Pereira JA, Lanzar Z, Clark JT, Hart AP, Douglas BB, Shallberg L, et al. PD-1 and CTLA-4 exert additive control of effector regulatory T cells at homeostasis. Front Immunol. 2023; 14: 997376.
91. Qin D, Zhang Y, Shu P, Lei Y, Li X, Wang Y. Targeting tumor-infiltrating tregs for improved antitumor responses. Front Immunol. 2024; 15: 1325946.
92. Charbonnier LM, Cui Y, Stephen-Victor E, Harb H, Lopez D, Bleesing JJ, et al. Functional reprogramming of regulatory T cells in the absence of Foxp3. Nat Immunol. 2019; 20: 1208-19.
93. Wang J, Gong R, Zhao C, Lei K, Sun X, Ren H. Human FOXP3 and tumour microenvironment. Immunology. 2023; 168: 248-55.
94. Chen Y, Colello J, Jarjour W, Zheng SG. Cellular metabolic regulation in the differentiation and function of regulatory T cells. Cells. 2019; 8: 188.
95. Kishore M, Cheung KCP, Fu H, Bonacina F, Wang G, Coe D, et al. Regulatory T cell migration is dependent on glucokinase-mediated glycolysis. Immunity. 2017; 47: 875-89.e10.
96. Hosseinzade A, Sadeghi O, Naghdipour Biregani A, Soukhtehzari S, Brandt GS, Esmaillzadeh A. Immunomodulatory effects of flavonoids: possible induction of T CD4+ regulatory cells through suppression of mTOR pathway signaling activity. Front Immunol. 2019; 10: 51.
97. Yan Y, Huang L, Liu Y, Yi M, Chu Q, Jiao D, et al. Metabolic profiles of regulatory T cells and their adaptations to the tumor microenvironment: implications for antitumor immunity. J Hematol Oncol. 2022; 15: 104.
98. Sun EJ, Wankell M, Palamuthusingam P, McFarlane C, Hebbard L. Targeting the PI3K/Akt/mTOR pathway in hepatocellular carcinoma. Biomedicines. 2021; 9: 1639.
99. Yi M, Zhang J, Li A, Niu M, Yan Y, Jiao Y, et al. The construction, expression, and enhanced anti-tumor activity of YM101: a bispecific antibody simultaneously targeting TGF-β and PD-L1. J Hematol Oncol. 2021; 14: 27.
100. MaruYama T, Kobayashi S, Shibata H, Chen W, Owada Y. Curcumin analog GO-Y030 boosts the efficacy of anti-PD-1 cancer immunotherapy. Cancer Sci. 2021; 112: 4844-52.
101. Jampasri S, Reabroi S, Tungmunnithum D, Parichatikanond W, Pinthong D. Plumbagin suppresses breast cancer progression

by downregulating HIF-1α expression via a PI3K/Akt/MTOR independent pathway under hypoxic condition. Molecules. 2022; 27: 5716.
102. Moldogazieva NT, Mokhosoev IM, Terentiev AA. Metabolic heterogeneity of cancer cells: an interplay between HIF-1, GLUTs, and AMPK. Cancers (Basel). 2020; 12: 862.
103. Yang F, Qin Y, Wang Y, Meng S, Xian H, Che H, et al. Metformin inhibits the NLRP3 inflammasome via AMPK/mTOR-dependent effects in diabetic cardiomyopathy. Int J Biol Sci. 2019; 15: 1010-9.
104. Miska J, Lee-Chang C, Rashidi A, Muroski ME, Chang AL, Lopez-Rosas A, et al. HIF-1α is a metabolic switch between glycolytic-driven migration and oxidative phosphorylation-driven immunosuppression of Tregs in glioblastoma. Cell Rep. 2019; 27: 226-37.e4.
105. Corcoran SE, O'Neill LAJ. HIF1α and metabolic reprogramming in inflammation. J Clin Invest. 2016; 126: 3699-707.
106. Tan CL, Kuchroo JR, Sage PT, Liang D, Francisco LM, Buck J, et al. PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. J Exp Med. 2020; 218: e20182232.
107. Vallion R, Divoux J, Glauzy S, Ronin E, Lombardi Y, Lubrano di Ricco M, et al. Regulatory T cell stability and migration are dependent on mTOR. J Immunol. 2020; 205: 1799-809.
108. Galgani M, De Rosa V, La Cava A, Matarese G. Role of metabolism in the immunobiology of regulatory T cells. J Immunol. 2016; 197: 2567-75.
109. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, et al. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory $CD4^+$ T cell subsets. J Immunol. 2011; 186: 3299-303.
110. Timilshina M, You Z, Lacher SM, Acharya S, Jiang L, Kang Y, et al. Activation of mevalonate pathway via LKB1 is essential for stability of T_{reg} cells. Cell Rep. 2019; 27: 2948-61.e7.
111. Feng R, Liu C, Cui Z, Liu Z, Zhang Y. Sphingosine 1-phosphate combining with S1PR4 promotes regulatory T cell differentiation related to FAO through Nrf2/PPARα. Scand J Immunol. 2023; 98: e13322.
112. Lim SA, Wei J, Nguyen TLM, Shi H, Su W, Palacios G, et al. Lipid signalling enforces functional specialization of T_{reg} cells in tumours. Nature. 2021; 591: 306-11.
113. Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, et al. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. Nat Immunol. 2020; 21: 298-308.
114. Wang J, Li Y. CD36 tango in cancer: signaling pathways and functions. Theranostics. 2019; 9: 4893-908.
115. Zhang Q, Zhu Y, Lv C, Fang Y, Liao M, Xia Y, et al. AhR activation promotes Treg cell generation by enhancing Lkb1-mediated fatty acid oxidation via the Skp2/K63-ubiquitination pathway. Immunology. 2023; 169: 412-30.
116. Ke XY, Zou M, Xu C. Lipid metabolism in tumor-infiltrating T cells: mechanisms and applications. Life Metab. 2022; 1: 211-23.
117. Liao X, Yan S, Li J, Jiang C, Huang S, Liu S, et al. CD36 and its role in regulating the tumor microenvironment. Curr Oncol. 2022; 29: 8133-45.
118. Stone TW, Williams RO. Interactions of IDO and the kynurenine pathway with cell transduction systems and metabolism at the inflammation–cancer interface. Cancers (Basel). 2023; 15: 2895.
119. Peyraud F, Guegan JP, Bodet D, Cousin S, Bessede A, Italiano A. Targeting tryptophan catabolism in cancer immunotherapy era: challenges and perspectives. Front Immunol. 2022; 13: 807271.
120. Shi H, Chapman NM, Wen J, Guy C, Long L, Dhungana Y, et al. Amino acids license kinase mTORC1 activity and Treg cell function via small G proteins Rag and Rheb. Immunity. 2019; 51: 1012-27.e7.
121. Yu HR, Tsai CC, Chang LS, Huang HC, Cheng HH, Wang JY, et al. L-arginine-dependent epigenetic regulation of interleukin-10, but not transforming growth factor-β, production by neonatal regulatory T lymphocytes. Front Immunol. 2017; 8: 487.
122. Long Y, Tao H, Karachi A, Grippin AJ, Jin L, Chang Y, et al. Dysregulation of glutamate transport enhances treg function that promotes VEGF blockade resistance in glioblastoma. Cancer Res. 2020; 80: 499-509.
123. Vilbois S, Xu Y, Ho PC. Metabolic interplay: tumor macrophages and regulatory T cells. Trends Cancer. 2024; 10: 242-55.

Cite this article as: Li N, Tian D. Targeting tumor-infiltrating regulatory T cells based on immunometabolism. Cancer Biol Med. 2026; 23: 186-200. doi: 10.20892/j.issn.2095-3941.2025.0645