Metabolism of Immune Cells in the Tumor Microenvironment

Jin G. Jung and Anne Le

Keywords
Immunometabolism · Tumor immunity · Metabolic competition · Metabolic barrier · CAR T lymphocytes

Abbreviations

ASCT2	Alanine, serine, cysteine transporter 2
CAFs	Cancer-associated fibroblasts
CAR	Chimeric antigen receptor
CTL	Cytotoxic T lymphocytes
ECM	Extracellular matrix
ERRα	Estrogen-related receptor alpha
FAO	Fatty acid oxidation
GLUT	Glucose transporter
GPCRs	G protein-coupled receptors
HIF1α	Hypoxia-inducible factor 1 α
HPSE	Heparanase
HSPG	Heparan sulfate proteoglycans
IFNγ	Interferon-gamma
IL	Interleukin
LDHA	Lactate dehydrogenase A
MCT	Monocarboxylate lactate transporters
MDSC	Myeloid-derived suppressor cells
mTOR	Mammalian target of rapamycin
NK cells	Natural killer cells
OXPHOS	Oxidative phosphorylation
PCK1	Phosphoenolpyruvate carboxykinase 1
PDK1	Pyruvate dehydrogenase kinase
PEP	Phosphoenolpyruvate
PGC1α	PPAR-gamma coactivator 1α
PHD	Prolyl-hydroxylase
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
SNAT	Sodium-coupled neutral amino acid transporter
TAM	Tumor-associated macrophages
T_{cm}	Central memory T cells
TCR	T-cell receptor
T_{eff}	Effector T cells
TILs	T-cell infiltrating lymphocytes
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
T_{reg}	Regulatory T cells

J. G. Jung
Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

A. Le (✉)
Department of Pathology and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Chemical and Biomolecular Engineering, Johns Hopkins University Whiting School of Engineering, Baltimore, MD, USA
e-mail: annele@jhmi.edu

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TRUCKs	T cells redirected for antigen-unrestricted cytokine-initiated killing
Tscm	Stem memory T cells

Key Points

- Tumor cells produce numerous substances to create an immunosuppressive tumor microenvironment.
- The tumor microenvironment physically constitutes a barrier against T-cell infiltration.
- Activated T cells reprogram OXPHOS and FAO to glycolysis and glutaminolysis.
- Tumors escape immunity via T-cell dysfunction or hyporesponsiveness by upregulation of several inhibitory receptors.
- Increased glucose uptake by cancer cells restricts T-cell function by decreasing mTOR activity.
- Treatments using immune checkpoint inhibitors increase extracellular glucose levels to improve T-cell infiltrating lymphocytes' function.

1 Introduction

The tumor microenvironment (TME) is a complex biological structure surrounding tumor cells and includes blood vessels, immune cells, fibroblasts, adipocytes, and extracellular matrix (ECM) [1, 2]. These heterogeneous surrounding structures provide nutrients, metabolites, and signaling molecules to provide a cancer-friendly environment. The metabolic interplay between immune cells and cancer cells in the TME is a key feature not only for understanding tumor biology but also for discovering cancer cells' vulnerability. As cancer immunotherapy to treat cancer patients and the use of metabolomics technologies become more and more common [3], the importance of the interplay between cancer cells and immune cells in the TME is emerging with respect to not only cell-to-cell interactions but also metabolic pathways. This interaction between immune cells and cancer cells is a complex and dynamic process in which immune cells act as a determinant factor of cancer cells' fate and vice versa. In this chapter, we provide an overview of the metabolic interplay between immune cells and cancer cells and discuss the therapeutic opportunities as a result of this interplay in order to define targets for cancer treatment. It is important to understand and identify therapeutic targets that interrupt this cancer-promoting relationship between cancer cells and the surrounding immune cells, allowing for maximum efficacy of immune checkpoint inhibitors as well as other genetic and cellular therapies.

2 Tumor Immunity and the Various Roles of Immune Cells

The immune system's antitumor activity is mainly carried out by tumor antigen-specific cytotoxic T lymphocytes (CTL), T effector (T_{eff}) cells, antibody-producing B cells, as well as antigen-presenting dendritic cells (DC), which lead to adaptive immunity by directly recognizing and eliminating cancer cells. Natural killer (NK) cells, macrophages, and NK-T cells also play crucial roles in suppressing tumor progression via a nonspecific immune response. Even though this defense system is well developed, the tumor often has the ability to develop an immunosuppressive microenvironment favorable to its progression. Specifically, myeloid-derived suppressor cells (MDSC), regulatory T (T_{reg}) cells, and tumor-associated macrophages (TAMs) are well-known players. These tumor-friendly immune cells suppress the settlement of tumor-infiltrating lymphocytes (TILs) by expressing essential amino acid (EAA)-degrading enzymes including arginase 1 (Arg1) and indoleamine-2,3-dioxygenase (IDO) [4–7], and inhibitors targeting Arg1 and IDO are being investigated in ongoing clinical trials [8, 9]. The TME is an environment composed of multifaceted components with tumor-friendly or antitumoral characteristics where there is strong competition for metabolites and nutrients. Studies have shown that T-cell-mediated adaptive response is a promising therapeutic strategy to strengthen the antitumor activity of the immune system [10–12].

2.1 Metabolic Competition and Tumor Immunity

With strong evidence showing how T lymphocytes infiltrate into the tumor niche and how checkpoint inhibitors or chimeric antigen receptor (CAR) T cells inhibit the growth of cancer cells, a new era of immunotherapy has just begun with successful clinical development [13]. However, cancer cells can escape immune recognition via "immunoediting," allowing cancer cell clones without detectable cancer antigens to dominate and escape from the pressure of immune checkpoint inhibitors [14].

Rapidly growing tumor cells require nutrients, oxygen, and essential metabolites to proliferate and, at the same time, create an immunosuppressive microenvironment. How immune cells and cancer cells share or compete in these harsh environmental conditions and how the TME alters immunometabolism are important questions to address. Specifically, it needs to be addressed how cancer cells and neighboring immune cells compete to take up nutrients and metabolites, which consequently influences signaling cascades, metabolic activities, and tumor progression.

Cancer-associated adipocytes: It is well known that adipocytes play an important role in communicating with cancer cells by excreting inflammatory factors, adipokines, and free fatty acids, which help cancer growth. In addition, immune cell functions are heavily regulated by lipids, lipoproteins, and cholesterol within the TME. For example, elevated levels of oxidized lipoproteins as a result of incorporation via scavenger receptors and formation of lipid droplets can compromise the ability of dendritic cells (DCs) to activate T cells by presenting tumor antigens [15, 16]. Also, it is well known that cancer cells instruct neighboring adipocytes to increase lipolysis [17].

Cancer-associated fibroblasts [18, 19]: It is reported that tryptophan catabolism by CAFs causes the starvation of immune cells and results in the production of kynurenine, an immunosuppressive metabolite [20]. Cancer cells also produce hydrogen peroxide (H_2O_2), which can lead to oxidative stress in CAFs. Oxidative stress is associated with impaired mitochondrial function, which results in upregulated glucose uptake and elevated reactive oxygen species (ROS) levels [21]. In addition, glucose is also a key metabolite for the antitumor activities of effector T (Teff) cells and M1 macrophages because aerobic glycolysis is necessary for their activation [22, 23].

Altered amino acid levels: Amino acids in the TME are not only a resource competed for by cancer and immune cells but also another metabolic checkpoint regulating antitumor immunity. For example, glutamine is a precursor for the tricarboxylic acid (TCA) cycle [24] and lipid synthesis in hypoxic cancer cells [25] and Teff cells [26]. As such, glutaminolysis, a series of biochemical reactions that start with the conversion of glutamine carbon to glutamate and aspartate, is essential for cancer cells by providing nutrients and metabolites through anaplerotic reactions, and leads to tumor cells' and TILs' competition for glutamine, the pathway's starting material [27–29]. Moreover, it is known that glutamine activates the mammalian target of rapamycin (mTOR) signaling cascades in T cells and macrophages and is important for protein O-GlcNAcylation and synthesis of S-2-hydroxyglutarate (S-2GH), a regulator of effector T (T_{eff}) cell function [30, 31]. Consequently, it was found that there is an upregulation of the major glutamine transporter alanine, serine, cysteine transporter 2 (ASCT2), also known as SLC1A5, for several types of cancer [32].

The proliferation of immune cells relies on growth factors for efficient nutrient utilization. For example, interleukin-2 (IL-2) promotes increased expression of glucose transporters (GLUT) and thus enhances glycolysis in activated T cells [33–36]. There is a question about how metabolites activate signaling pathways to induce changes in immune cell functions. A classic example is the binding of metabolites and energy substrates to G protein-coupled receptors (GPCRs) [37]. For example, succinate leads to increased chemotaxis and activation of dendritic cells after toll-like receptor (TLR) agonist treatment by binding to the succinate receptor GPR91 [38]. On the other hand, adenosine, by binding to A2B and A2A adenosine receptors, leads to

increased interleukin 4 (IL-4)-induced M2 macrophage activation [39]. Moreover, it is recently reported that there is a significantly reduced arginine level in the TME as a result of inducible nitric oxide synthase (iNOS) and arginase expressed by myeloid-derived suppressor cells, indicating that rapid dynamic changes of amino acids can happen in the TME [40].

2.2 Antitumor T-Cell Metabolisms in the TME

As T cells play a critical role in antigen-specific adaptive immunity against the tumor, it is fundamentally important to understand T-cell biology. T lymphocytes respond to the presence of antigens and evolve rapidly. This response first requires T-cell growth; then their drastic expansion, differentiation, and death; and lastly, the formation and preservation of the memory of the immune response.

T lymphocyte proliferation in the TME requires a switch in its metabolism. While naïve T cells utilize fatty acid β-oxidation, activated T cells mainly use glycolysis, pentose phosphate pathway, and glutaminolysis [41, 42]. Additionally, it is reported that distinct transcriptional programs and signaling pathways are involved in this metabolic shift, including the transcription factor c-Myc [43, 44], estrogen-related receptor alpha (ERRα) [41, 45, 46], phosphatidylinositol-3-OH kinase (PI(3)K), and GLUT1-dependent Akt pathways [45]. This significant metabolic reprogramming of activated T cells is required for their proliferation and expansion. Consistently, it is also reported that activated T cells switch from oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to glycolysis and glutaminolysis, which are characteristics of Teff cells, induced by antigenic stimulation through the T-cell receptor (TCR) and engagement of CD28 with a ligand on antigen-presenting cells (APC) [26]. Although glycolysis produces less ATP than OXPHOS, it is very efficient at producing biosynthetic precursors [47], which can further support the rapid proliferation and pro-inflammatory functions of Teff. Moreover, it is consistent with the findings that depletion of GLUT1 impaired T-cell proliferation and functions [36], while elevated expression of GLUT1 increased Teff cell functions [48]. In addition, demands for nutrients, such as glucose, glutamine, and other amino acids, lead to upregulations of transporters in T cells, including GLUT1 [36, 45, 49], glutamine transporters and sodium-coupled neutral amino acid transporters 1 and 2 (SNAT1 and SNAT2) [50], and monocarboxylate lactate transporters MCT1 and MCT4 to export lactate produced via aerobic glycolysis [51].

This metabolic shift from OXPHOS and FAO to glycolysis and glutaminolysis during T-cell activation is mediated by several crucial regulators. It is reported that TCR directly induces PI3K/Akt/mTORC1 and *MYC* pathways, which not only activate effector T cells but are also crucial for their proliferation and biological functions [26]. Indeed, an activated mTOR pathway promotes glycolysis by upregulating c-*MYC* and hypoxia-inducible factor 1α (HIF1α) [41, 45, 48, 49, 52, 53]. *MYC* then induces the transcriptional factor AP4, which further upregulates glycolytic enzyme gene expressions [54]. Moreover, increased HIF1α expression and activity upregulate pyruvate dehydrogenase kinase (PDK1) and lactate dehydrogenase A (LDHA), leading to increased aerobic glycolysis and decreased OXPHOS [55, 56], thus switching pyruvate away from the TCA cycle to lactate production. HIF1α also promotes glycolysis by upregulating GLUT1 and MCT4 expression, in addition to glycolytic enzymes and regulators [57].

After fulfilling their duties, activated T cells undergo apoptosis during a time period called the contraction phase [58], while T_{reg} cells and memory T (T_{mem}) cells, by using lipid oxidation for energy production, remain in peripheral tissues or secondary lymphoid organs without undergoing apoptosis [48, 57, 59, 60].

2.3 Cancer Cells' Impacts on T-Cell Metabolism in the TME

It is well known that T-cell dysfunction, or hyporesponsiveness, can result in tumors escaping immunity. This dysfunction or hyporesponsiveness is due to exhaustion and senescence of T cells [61]. For instance, tumor cells are shown to express indoleamine 2,3-dioxygenase (IDO), an enzyme that results in decreased tryptophan levels and inhibition of T-cell proliferation [62, 63]. Lactate produced by tumor cells can also lead to reduced T-cell function by blocking their lactate export [64]. Intracellular lactate accumulation impairs their aerobic glycolysis and thus limits their function [65].

Moreover, increased glucose uptake and consumption by cancer cells [66] impair T-cell function by decreasing their mTOR activity, glycolysis, and INF-γ production. These negative consequences on T cells help promote tumor progression, which is also facilitated by decreased cytokine production due to the lack of glucose in the microenvironment. It is also supported by the fact that many types of tumors have high glycolysis rates [67, 68]. Moreover, lack of glucose impairs IFN-γ production of T cells and proinflammatory signals in macrophages [36, 65, 69]. In addition, increased glycolysis rate in tumor cells as a result of the overexpression of the glycolytic enzyme hexokinase 2 (HK2) reduced glucose uptake and IFN-γ production in TILs, which led to a more tumor-friendly microenvironment [69, 70].

2.4 Cancer Cell-Induced Metabolically Harsh Environment Impairs T-Cell Function

As the tumor grows larger, (1) oxygen supply becomes limited, thus creating a hypoxic condition; (2) nutrients become deficient; and (3) the microenvironment becomes acidic. Recent findings suggest that these harsh metabolic states significantly disrupt T-cell function. Therefore, the influence of cancer cell metabolism on the TME may directly control the metabolic pathways in surrounding T cells [71]. The tumor microenvironment physically constitutes a barrier against T-cell infiltration, as it is a compact structure with tight interactions among cancer cells, fibroblasts, immune cells, and ECM. Indeed, tumor cells generate numerous substances to create an immunosuppressive microenvironment. For example, hypoxic cancer cells release prostaglandin E2 (PGE2) and adenosine, which can result in T lymphocyte proliferation inhibition by activating G protein-coupled receptors (GPCR) and protein kinase A [72]. Among the GPCRs, chemokine (C-X-C motif) receptor 3 (CXCR3) and chemokine (C-C motif) receptor 5 (CCR5) are often expressed in active lymphocytes that have infiltrated the tumors in melanoma, breast, and colorectal cancers [73] (Fig. 1).

In order to reach tumor cells and to enhance the efficacy of immunotherapy, T lymphocytes have to degrade the ECM and heparan sulfate proteoglycans (HSPGs) [74]. It is reported that chimeric antigen receptor (CAR) T cells need to release heparanase (HPSE) to successfully degrade HSPGs, which then allows T cells to gain access to the solid tumor [75] (Table 1 and Fig. 1).

3 Targeting the Metabolism of Immune Cells for Cancer Treatment

Accumulating evidence from the past decade indicates that metabolic reprogramming greatly affects T cells. Indeed, when T cells recognize antigens, they are activated to proliferate and produce effector molecules to eliminate the foreign antigens. During this course of the immune response, immune cells respond to changes in the metabolic microenvironment, which serves as a "metabolic checkpoint" responsible for connecting the metabolic states with signaling pathways in immune cells, which further determines their immune functions [47]. Accordingly, metabolic reprogramming of cells, such as a switch from OXPHOS and FAO to glycolysis and glutaminolysis in naïve and memory T cells, helps provide energy and other building block materials to generate new biomass. The manipulation of metabolic enzyme expressions helps T cells adapt in the tumor-suppressive microenvironment and

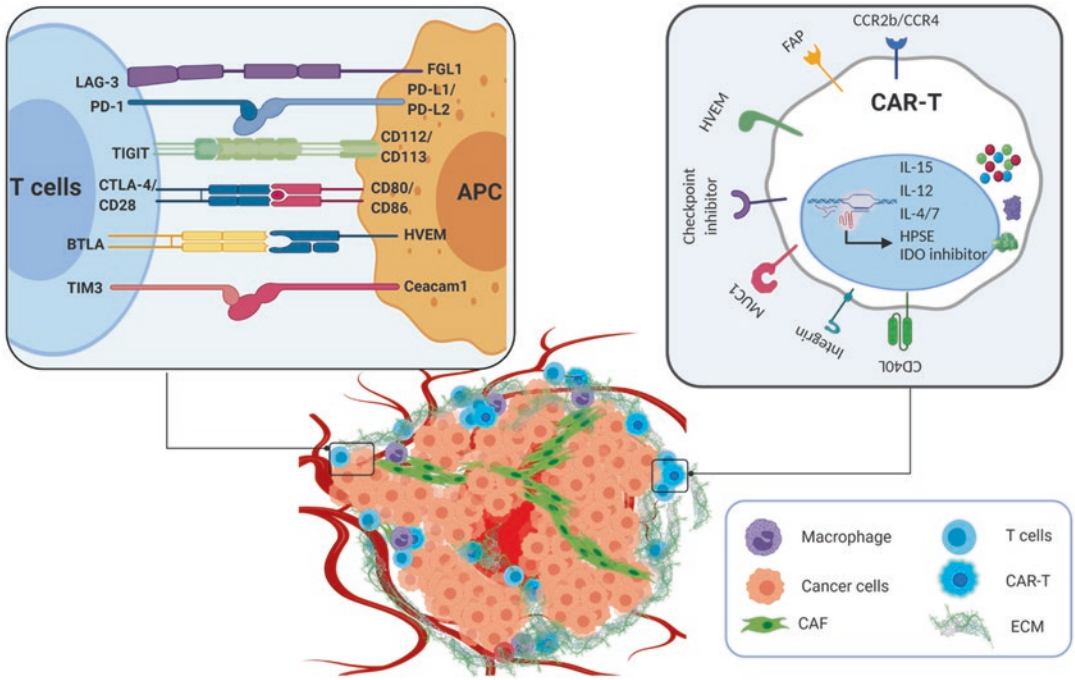

Fig. 1 Potential immunometabolism-targeting strategy in the TME. *APC* antigen-presenting cells, *CAR T* chimeric antigen receptor T cell, *CAF* cancer-associated fibroblast, *ECM* extracellular matrix

restore their functions. Specifically, overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1) results in a high level of the glycolytic metabolite phosphoenolpyruvate (PEP). High PEP level then enhances T-cell effector functions through T-cell receptor-mediated Ca^{2+}-dependent nuclear factor of activated T-cell (NFAT) signaling. PCK1-overexpressing T cells inhibited melanoma tumor growth in vivo [70]. Another example is the oxygen-sensing prolyl-hydroxylase (PHD) proteins, which, as oxygen sensors in T cells, support cancer metastasis to the lung. Indeed, targeting T-cell-intrinsic PHD proteins resulted in increased antitumor immunity [112]. Also, as TILs usually have impaired mitochondrial function after infiltrating the tumors, reactivation of PPAR-gamma coactivator 1α (PGC1α) by suppressing Akt signaling in these T cells can induce mitochondrial biogenesis. Thus, increasing the expression of PGC1α in these T cells also activates their functions [113]. These approaches may improve antitumor immunity for adoptive T-cell therapy, which is a personalized therapy for cancer via T-cell manipulation [70, 112, 113].

3.1 The Metabolism of the Immune Checkpoint Blockades

When T cells infiltrate the TME, they gradually lose several abilities, including responsiveness to T-cell receptor (TCR) stimuli and production of antitumor cytokines, in a phenomenon referred to as T-cell exhaustion or hyporesponsiveness. This is the result of the upregulation of several inhibitory receptors such as PD-1, LAG3, TIGIT, and CTLA-4 that make T cells less sensitive to tumor antigens [114]. In particular, the PD-1:PD-L1 axis and CTLA-4 are critical immune checkpoints for T cells, and targeting these receptors breaks down the cross talk between cancer cells and exhausted T cells. This result is supported by numerous clinical successes of immune checkpoint inhibitors, including ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab-rwlc [115].

Interestingly, glucose deprivation caused by rapid uptake by actively growing cancer cells and glucose competition between cancer cells and

Table 1 Tumor microenvironment-related obstacles and possible solutions (modified from [76])

Obstacle	Factor	Solution	References
Tumor stroma	Cancer-associated fibroblast	Anti-FAP CAR T cells	[77]
	Heparan sulfate proteoglycan	Heparanase-secreting CAR T cells	[75]
	ECM-targeting CAR T	Oncolytic virus	[78]
Tumor antigen	integrin	Integrin αvβ6, integrin β-targeting CAR T	[79, 80]
	MUC1	Tumor-expressing MUC1-targeting CAR T	[81, 82]
Cytokines and enzymes	Immunosuppression of the TME	TRUCK T cells expressing IL-12, IL-15, IL-18	[83]
	TGF-β	TGF-β dominant-negative CAR T cells	[84]
	IL-4	4/7 ICR CAR T cells (IL-4 exodomain)	[85]
	IL-7	CCL19 CAR T cells	[86]
	Adenosine	A2AR receptor antagonist	[87, 88]
	CCR	CCR2/4-targeting CAR T	[89]
Metabolism and hypoxia	CD73	CD73 inhibitor	[90]
	ROS and H2O2	Catalase CAR T	[91]
	Indolamine-2,3 dioxygenase (IDO)	IDO inhibitor	[92]
	Protein kinase A	RIAD-CAR T	[93]
	High levels of antioxidants	N-acetyl cysteine	[94]
Immune inhibitory checkpoints	CTLA-1	CTLA-4 inhibitor	[95]
		CTLA-4 knockout in CAR T	[96]
		Anti-CTLA-1 antibody-producing CAR T	[95]
	PD-1	PD-1 inhibitor	[97]
		PD-1 KO in CAR T	[98]
		PD1-CD28 CAR T	[99]
		Anti-PD-1 antibody-producing CAR T	[99]
	LAG-3	Blockade of LAG-3 and PD-1	[100]
	TIM3	TIM3 KO in CAR T	[100]
	BTLA-4	BTLA-4 inhibitor	[100]
		Blockade of BTLA-4 and PD-1	[101]
		HVEM-targeting CAR T	[102]
	A2AR	A2AR antagonist	[88]
	TIGIT	Blockade of TIGIT and PD-1	[103]
	CD40L	CD40L-CAR T	[104]
Immunosuppressive cells	MDSC	CXC15-CXCR2 inhibitor	[105]
	T_{reg}	ALTRA-CAR T	[106]
		Genetic depletion and anti-PD-L1 blocking Ab of T_{reg}	[107]
		Use of IL-2, IL-7, and IL-21 with CAR T	[108, 109]
	TAM	Induction of TAM to produce nitric oxide	[110]
	iDC	Expression of IL-18 by CAR T	[110, 111]

other cells in the TME further upregulates PD-1 expression [114, 116]. In fact, PD-1 activation leads to suppressed T-cell receptor (TCR), PI3K, and mTOR signaling in T cells and reduced glycolysis, which may lead to increased accumulation of regulatory CD4 (T_{reg}) cells in the TME

[117–119]. If PD-L1 on the surface of tumor cells binds to PD-1 on T cells, referred to as the engagement of PD-1, T-cell proliferation, cytokine production, and cytolytic function are inhibited, which promotes cancer cell proliferation [120]. It has also been shown that the degree of PD-L1 expression correlates with glycolysis rates, as well as the expression levels of glycolytic enzymes [116]. Moreover, α-PD-L1 antibody treatment increases extracellular glucose levels in vivo, which results in improved TIL function and subsequently reduced tumor growth. Indeed, intrinsic PD-1 expression promotes mTOR signaling and tumor growth [121], while blockade of PD-1 signaling activates glycolysis and anabolic pathways in exhausted T cells via mTORC-1 [69, 122]. Thus, this metabolic shift provides the rationale for the clinical development of combination therapy with immune checkpoint blockade and mTOR inhibitors. Indeed, multiple clinical trials are under investigation with those drug combinations in patients with TNBC and renal cell carcinoma (NCT03805399, NCT04203901). Collectively, these results imply that the most promising therapy should target the co-inhibitory receptor-to-ligand interactions and re-sensitize exhausted T cells in the TME.

3.2 The Metabolism of Chimeric Antigen Receptor (CAR) T Cells

Recent clinical progress with genetically engineered chimeric antigen receptor (CAR) T cells for cancer therapy opens up a new era of cell/gene therapy. However, its success is limited thus far to acute lymphoblastic leukemia (ALL) and lymphoma, whereas it shows less promising results for solid tumor treatment [72]. It is widely accepted that the major cause of the limited efficacy of CAR T cells is the poor accessibility of T cells to the TME and the low-nutrient, hypoxic environment that provides suboptimal conditions for T-cell proliferation and cytokine production [123]. Thus, CAR T-cell infiltration into the tumor is a critical step to enhance their antitumor efficacy in solid tumors (Fig. 1).

The lack of therapeutic effects of CAR T cells in solid tumors is due, in part, to the immunosuppressive TME, which acts as a critical barrier. As such, new strategies to increase CAR T cells' accessibility to TME in solid tumors have been proposed. For example, stabilization of HIF1α under hypoxic conditions regulates cellular metabolism, which is a critical feature in the hypoxic TME. A recent study found that targeting an oxygen-sensitive subdomain of HIF1α enhances the CAR-T activity in solid tumors [124]. Another example of new strategies for CAR T therapy is the targeting of heparanase (HPSE). Stroma and tumor cells in the TME are linked together through the ECM which contains a considerable amount of heparan sulfate proteoglycan (HSPG) [75]. To explore whether HSPG can be targeted in solid tumors, Caruana et al. generated HPSE-expressing CAR T cells that showed ECM degradation ability in solid tumors, which resulted in increased infiltration and antitumor activity [75]. This approach may imply the therapeutic benefits of the use of CAR T immunotherapy coupled with HPSE degradation to access tumor niches.

Another approach of engineering CAR T cells to target solid tumors is the development of the nuclear factor of activated T cells, which is referred to as T cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs). For instance, engineered CAR T cells with several cytokines, including interleukin-7, -12, -15, and -18, are being explored for TRUCKs [125, 126]. The underlying physiological functions of these interleukins in CAR T-cell therapies are summarized in the reference [126]:

- Interleukin-2: proliferation of T-cell differentiation of Te_{ff}, development of T_{reg} in thymus
- Interleukin-4: differentiation of Th2 and Th9 cells, survial of B-cells and T-cells
- Interleukin-7: development of T-cell in thymus, survival of and homeostasis in memory and naïve T cells
- Interleukin-9: mast cell proliferation, increased antitumor immunity
- Interleukin-15: development of $CD8^+$ T-cell memory, survival of and homeostasis in $CD8^+$ T-cells

- Interleukin-21: suppression of T_{reg}, survial and proliferation of $CD4^+$ Th17 cells

Among them, engineered CAR T cells with IL-2, IL-7, IL-15, and IL-21 NFATs are being investigated in clinical trials [126] (Table 1 and Fig. 1).

In addition, it is also known that cytokines can be manipulated to control the metabolism of stem memory T cells (T_{SCM}) and central memory (T_{cm}) T cells. Of note, T-cell activation by interleukin families, including IL-15 and IL-17, leads to an increased T_{SCM}-like phenotype as well as increased interferon-gamma (IFNγ), tumor necrosis factor alpha (TNFα), and IL-2 production [127]. Moreover, it has been reported that IL-15 activates fatty acid oxidation (FAO) and mitochondrial spare respiratory capacity (SRC) as an alternate way for energy production in T cells [60]. Taken together, IL-15 may provide therapeutic benefits in the form of T memory cell differentiation and mitochondrial metabolism [60]. In addition to mitochondrial metabolism, manipulation of ion and pH levels in the tumor microenvironment, such as decreasing the concentration of potassium, can also enhance T-cell antitumor activity [128]. As such, these metabolism-targeting approaches will provide the rationales for future clinical developments and therapeutic use of CAR T-cell immunotherapy for cancer patients.

4 Conclusion

The immunosuppressive microenvironments in solid tumors are physically and functionally hostile for immune cells, including immune checkpoint inhibitors and CAR T cells. The reasons for less promising efficacy of immunotherapies vary and include the immune cells' poor accessibility to tumor cells in the TME due to physical and metabolic barriers, including a lack of nutrients and acidosis. In order to improve the therapeutic efficacy of immunotherapies, the tightly controlled microenvironment has to be modified by targeting the metabolic vulnerability of cancer cells. This includes either targeting metabolic enzymes to regulate the metabolism of cancer cells or disrupting the tumor-friendly microenvironment. As metabolism is fundamental for biological and cellular functions, targeting the tumor microenvironment itself or modifying T-cell metabolism is a promising strategy to improve current treatment efficacy.

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