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Reenergizing T cell anti-tumor immunity by harnessing immunometabolic checkpoints and machineries

Ping-Chih Ho[1,2] and **Susan M. Kaech**[3]

[1]Department of Fundamental Oncology, University of Lausanne, Lausanne, Vaud 1066, Switzerland [2]Ludwig Lausanne Branch, University of Lausanne, Lausanne, Vaud 1066, Switzerland [3]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06519, USA

Abstract

T cells patrol our bodies preventing pathogenic infections and malignant cell outgrowth. However, T cells must be properly controlled because aberrant or persistent T cell responses can damage tissues and contribute to autoimmune diseases and other chronic inflammatory diseases including metabolic syndrome. One regulatory mechanism utilized in immune cells is immunometabolic regulation, which ensures immune cells properly respond to systemic and peripheral metabolic cues. Recent work has suggested that deregulated metabolism in tumor cells creates a microenvironmental barrier for mounting effective anti-tumor immune responses. Here, we discuss how tumor cells evade immunosurveillance by modulating metabolic checkpoints in immune cells and discuss how memory T cells could provide effective anti-tumor responses by sustaining metabolic fitness and longevity.

Introduction

Tumor-infiltrating lymphocytes can play critical roles in regulating tumor outgrowth [1,2] and numerous forms of immunotherapies are now under investigation to enhance anti-tumor immune responses. Approaches such as vaccination and adoptive T cell transfer can expand the tumor-specific T cell population, but often in solid tumors, such beneficial responses are hindered by the immunosuppressive tumor microenvironment (TME) [2–6]. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoint blockade have been shown to successfully boost host anti-tumor immunity in a restricted portion of patients [2,7]. Intriguingly, this indicates that it is possible to subdue immunosuppressive features of the TME. Therefore, understanding in detail the mechanisms exploited by tumor cells to negate anti-tumor responses is essential for developing new interventions to work alone or with current cancer immunotherapies.

*correspondence: Ping-Chih Ho and Susan M. Kaech, ping-chih.ho@unil.ch (Ping-Chih Ho), susan.kaech@yale.edu (Susan M. Kaech).

Tumor cells display abnormal metabolic activities; consuming nutrients and generating metabolites differently compared to non-proliferative normal tissues and benign lesions [1,8]. These metabolic alterations, including Warburg glycolysis and *de novo* fatty acid synthesis, support the unrestricted proliferation and survival of tumor cells [8]. However, these intrinsically beneficial metabolic changes in tumor cells can also have extrinsic effects and modulate neighboring cell behavior through nutrient competition and exchanges of metabolic intermediates [9–14]. Details on how particular metabolic processes regulate immune cell function are covered elsewhere in this issue. Therefore, this piece will focus on how altered metabolic states of the tumor cells act extrinsically to influence the types of tumor infiltrating immune cells, their metabolic activities and functions, and how targeting T cell memory pathways could be an attractive strategy to sustain anti-tumor immunity.

Anti-tumor immune responses are impaired by the altered nutrient state of the tumor microenvironment (TME)

Acidosis and lactic acid in the TME

Otto Warburg discovered that, in normoxic conditions, rapidly growing tumor cells produce copius amounts of lactic acid from glucose, a process known as the Warburg glycolysis [15]. This process allows tumor cells to accumulate the metabolic intermediates, such as nucleotides and amino acids, to support macromolecule production necessary for cell division [15,16]. However, the lactic acids produced by tumor cells during this process acidify the TME and both the lower pH or the direct effects of lactate/lactic acid can modulate the neighboring immune cells in the TME [17–19]. Particularly in hypoxic areas in tumors where the low diffusion rates of oxygen further enhances tumor cell glycolysis and TME acidosis [16,20–22]. Lactic acids are co-transported with the proton concentration gradient through the monocarboxylate transporter (MCT). Therefore, MCT inhibitors, acting upon tumor cells, may neutralize acidosis and prevent lactic acid transport into T cells, thereby improving T cell functions [18,19]. However, it is possible that MCT inhibitors could also impair anti-tumor T cell responses because the reduced dissipation of lactic acids within activated T cells could raise intracellular pH to toxic levels [14,23,24]. Lactic acid is directly suppressive to T cell effector functions such as IFNγ and Granzyme B production [18,24,25] Lactate can also induce VEGF production in tumor associated macrophages that promotes angiogenesis and tumor growth [14] Intriguingly, the mobility of $CD8^+$ and $CD4^+$ T cells could be differentially suppressed by lactic acid and sodium lactate due to the expression of T cell subtype-specific transporters [18]. Additionally, a recent report showed that tumors with low lactate dehydrogenase A (LDHA) activity were more infiltrated by T and NK cells [24] These findings suggest that increased lactic acid production by tumors aides in tumor evasion by hindering T cell mobility and effector functions in the TME. Thus, targeting lactic acids and lactate in the tumor microenvironment may be an attractive strategy to unleash T cell and macrophage anti-tumor responses.

Glucose and amino acids deprivation in the tumor microenvironment impairs anti-tumor immunity

Effector T cells utilize aerobic glycolysis and increased amino acid metabolism to support proliferation and production of effector molecules by modulating signaling cascades and transcriptional and translational events [26]. However, oncogenic mutations and hypoxia profoundly enhance the rate and ability of tumor cells to uptake glucose [15], which could in turn, restrict glucose availability to infiltrating T cells and other neighboring cells, such as antigen-presenting and endothelial cells. Glucose restriction in T cells promotes T cell dysfunction and impairs calcium signaling, mechanistic target of rapamycin (mTOR) activity, translation of effector molecules, and survival through various metabolic regulations [10,26–29]. Moreover, PD-1 signal suppresses glycolytic metabolism whilst stimulating fatty acid oxidation in T cells to further prevent T cells from achieving the metabolic demands required to sustain anti-tumor responses [30,31]. Recent studies support the notion that tumor infiltrating T cells fail to acquire sufficient glucose in certain types of tumors and that tumor cells displaying higher glycolytic activity are prone to escape immunosurveillance [12,13]. Intriguingly, boosting glycolytic activity by stabilizing HIF1α through PHD- or VHL-deficiency or metabolic rewiring tumor-specific T cells by overexpressing phosphoenolpyruvate carboxykinase 1 (PCK1) improved anti-tumor T cell activities [12,32,33]. These findings reveal ways by which the glycolytic activity of tumor cells can facilitate immune evasion. Thus, targeting oncogenic mutations that sustain anabolic metabolism in tumor cells (such as oncogenic $Braf^{V600E}$ in melanoma or EGF receptor tyrosine kinase in head and neck squamous cell carcinoma and non-small-cell lung cancer), might indirectly lead to improved T cell anti-tumor responses and metabolic fitness in part due to the suppressive effects of these drugs on tumor cell glycolysis [34–36]. Interestingly, the expression of ligands for co-inhibitory receptors, such as PD-L1 and B7-H3, could enhance Warburg glycolysis and glucose uptake rates in tumor cells [13,37,38]. In these studies, targeting these ligands of co-inhibitory receptors could suppress glycolytic activity of tumor cells. Therefore, in addition to relief the inhibitory signal in T cells PD-1 blockade may synergize with treatments targeting ligands of co-inhibitory receptors to boost the metabolic fitness of infiltrating T cells.

Amino acid metabolism is also highly regulated in the TME by tumor cells and other immunoregulatory cells. For example, tumor cells, M2-like TAMs and myeloid-derived suppressor cells (MDSCs) often have increased Arginase 1 (Arg1) and indoleamine-2,3-dioxygenase (IDO) activity that metabolize arginine and tryptophan, key amino acids necessary for T cell receptor signaling, effector functions, proliferation and survival [26,39–44]. Additionally, IDO catabolizes tryptophan into kynurenine [45], a metabolite that promotes $CD4^+$ Treg differentiation and immunosuppression of effector T cells [46–48]. Given the immunosuppressive nature of Arg1 and IDO, inhibitors of Arg1 and IDO could mount effective anti-tumor T cell responses and suppress tumor progression in murine tumor models and how these inhibitors unleash host anti-tumor responses in patients are undergoing intensively investigations in multiple clinical trails [49]. In addition, increased glutaminolysis in tumor cells is critical to replenish metabolites through anaplerosis, which could result in deprivation of glutamine to tumor infiltrating T lymphocytes. Since glutamine metabolism in T cells controls T cell activation and self-renewal by enhancing mTOR

activation, protein O-GlcNAcylation, and is also a key substrate for the formation of 2-ketoglutarate (2-KG) and *S*-2-hydroxyglutarate (*S*-2-HG) that regulate effector T cell functions and differentiation [50–52], inhibiting glutaminolysis and glutamine transporters in tumor cells might induce anti-tumor responses and synergize with other cancer immunotherapies. Taken together, these findings indicate that the TME could also suppress immunisurveillance by quenching amino acid availability to T cells.

Lipid metabolism: a new metabolic regulator for immune evasion

Prolific lipogenesis via *de novo* fatty acid synthesis and fatty acid uptake are other hallmarks of transformed cells that promote tumor progression, metastasis, and resistance to cellular stress [53,54]. Indeed, targeting lipogenesis in tumor cells suppresses tumor progression [53,55–57], but it remains unclear whether increased lipid synthesis in tumor cells impacts the neighboring cells in the TME. It is possible that free fatty acids accumulate in the TME by tumor cell necrosis, increased lipolysis of TAGs by lysophosphatidyl lipase (LPL) or local adipocytes may enhance the persistence or survival of lipid-oxidizing $CD4^+$ Tregs and MDSCs, decrease antigen-presentation ability of dendritic cells, and/or suppress the effector functions of cytotoxic $CD8^+$ and T_H1 $CD4^+$ T cells [27,58,59]. These findings suggest that lipid metabolism in tumors could be a regulator for anti-tumor immunity. Intriguingly, emerging evidence revealed that short-chain fatty acids (SCFAs) could promote Tregs formation but middle- and long-chain fatty acids support differentiation of Th1 and Th17 cells in gut [60]. Thus, we postulate that in the TME, tumor cells may disarm T cell anti-tumor immunity by feeding unique fatty acids to reorient their effector functions and differentiation states. Taken together, it will be critical for future research to determine how immune cells adapt their immune functions in response to particular species of lipid and lipid composition, both *in vitro* and *in vivo*.

Superior anti-tumor immunity induced by tumor-specific memory T cells

Developing long-lived immunity to cancer is an ultimate goal for effective cancer therapy and may reduce incidence of recurrence in patients. Given that adoptive cell transfer (ACT) is a strategy to select and manipulate cellular activities of tumor-specific CTLs, ACT becomes a platform to understand the qualitative difference of the *in vitro* expanded tumor-specific CTLs. Interestingly, in contrast to transferring effector $CD8^+$ T cells that have a limited lifespan, the same amount of memory $CD8^+$ T cells elicit stronger anti-tumor responses and give prolonged protection for tumor recurrence [2]. These findings suggest that a promising anti-tumor strategy would be to manipulate the memory phenotype of tumor-specific $CD8^+$ T cells during the *in vitro* expansion of transferred T cells. In contrast to utilizing anabolic metabolism in effector $CD8^+$ T cells, memory $CD8^+$ T cells prefer to engage catabolic metabolism, including increased oxidative metabolism and fatty acid oxidation, to support metabolic demands [26,61–63]. Therefore, it may be possible to force the generation of memory $CD8^+$ T cells by manipulating the metabolic pathways during *in vitro* T cell expansion. Indeed, several recent studies have shown that treating T cells with 2-deoxyglucose or an Akt inhibitor produces memory-like T cell populations with stronger anti-tumor responses and survival potential [64,65]. In addition, increasing L-Arginine availability could increase T cell mitochondrial respiration in an *in vitro* culture and these T

cells display memory phenotypes and superior anti-tumor responses [66]. These findings lend credence to the idea that tailoring metabolic program of transferred T cells may elicit different anti-tumor responses, and further indicates that memory $CD8^+$ T cells may adapt their metabolic demands to the nutrient composition in the TME. In support of this possibility, a recent study using chimeric antigen receptor (CAR) T-cells discovered that the newest generation of CAR allows T cells to increase growth and survival by engaging a metabolic phenotype seen in memory $CD8^+$ T cells [67]. These studies indicate that metabolically modulated adoptively transferred T cells, including endogenous and CAR T cells, can achieve longer-lasting and possibly more potent anti-tumor responses; however, it remains unclear why memory $CD8^+$ T cells can perform better in the TME. Since mitochondrial activity and fatty acid oxidation support the metabolic demands of memory T cells [61–63], we postulate that these properties may augment the persistence and proliferative capacity of memory T cells in the TME. Indeed, declined mitochondrial content and inability to engage mitochondrial biogenesis in tumor infiltrating $CD8^+$ T cells was recently shown to result in metabolic insufficiency and poor anti-tumor responses [68]. Intriguingly, overexpressing peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC1α) in tumor antigen-specific $CD8^+$ T cells could enhance their anti-tumor responses by promoting mitochondrial biogenesis [68]. Since increasing mitochondrial content is a metabolic hallmark of memory T cells, it is likely that overexpression of PGC1α could skew activated $CD8^+$ T cells into a memory-like phenotype. In addition to mitochondrial content, memory T cells have been reported to display fused mitochondrial structure and promoting mitochondrial fusion in T cells could lead to a memory-like phenotype and stronger anti-tumor activities [69]. Interestingly, the formation of tubular and fused network of mitochondria has been shown to allow fibroblasts to adapt their metabolic demands during nutrient starvation [70]. Thus, in addition to anabolic metabolism, the mitochondrial fitness and activity in memory T cells might also play critical roles to sustain their survival and proliferation in the TME (Figure 1). Altogether, these findings indicate that targeting metabolic regulations of memory T cells could be applied in cell-based immunotherapies to elicit superior anti-tumor responses and long-lasting protection for tumor recurrence. However, an important direction for future studies is to determine if and how memory T cells and secondary effector T cells derived from memory T cells could resist the metabolic crisis that can occur in the TME.

Conclusions and future directions

We are at a remarkable point in the new era of immunotherapy and cancer immunology, and as we deepen our understanding of immunometabolism by elucidating how particular metabolic pathways and nutrients influence T cell differentiation, function and trafficking, this may reveal new types of drugs and/or treatments that could be combined with other forms of immunotherapy. Even the handful of recent reports described herein offers several clinically-viable possibilities for new cancer treatments that could be implemented in the very near future. Considering memory T cells provide superior anti-tumor immunity, it is critical to determine how metabolic pathway(s) of memory T cells support their survival, function and proliferative capacity in the TME. It would also be critical to examine how the TME impairs the mitochondrial fitness of tumor infiltrating T cells and determine how

mitochondria of T cells could orchestrate desired anti-tumor responses. The knowledge gained from these studies would serve as a springboard for tailoring T cell-based cancer immunotherapies.

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Highlights

- Metabolic stress in tumors impairs T cell anti-tumor immunity.
- Memory T cells could be optimal cell type to sustain metabolic fitness in tumors.
- Skewing memory T cell formation is a promising strategy in adoptive cell therapy.
- Mitochondrial metabolism may be critical to sustain T cell tumoricidal functions.

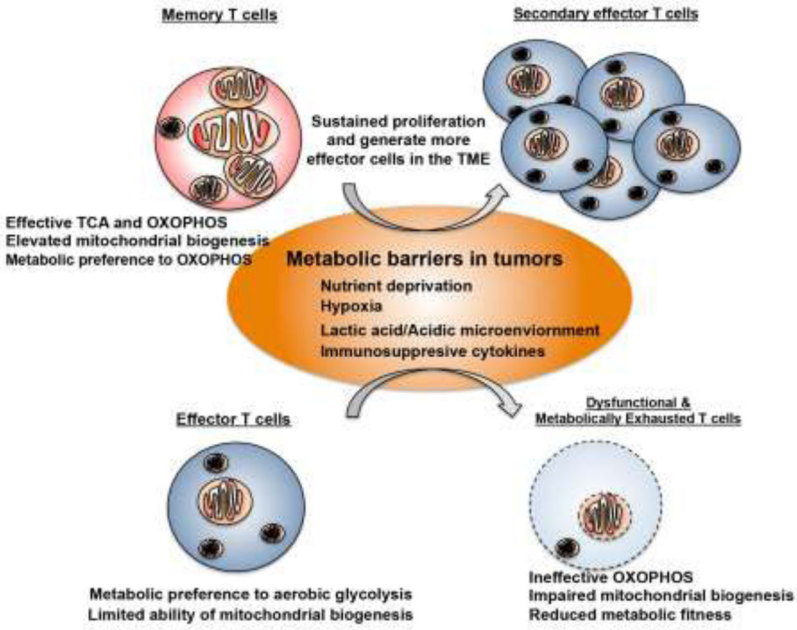

Figure 1. Mitochondria-mediated metabolic support in memory T cell anti-tumor immunity

The metabolic stresses in the tumor microenvironment, including nutrient deprivation, hypoxia, acidic environment and immunosuppressive cytokine milieu, suppress anti-tumor responses and metabolic fitness in effector T cells. These microenviornmental barriers could affect mitochondrial mass and activity that lead to impaired TCA cycle and changes in bioenergetic programm. However, memory T cells might maintain their anti-tumor immunity by resisting to these microenvironmental barriers or sustaining their mitochondrial mass and functions.