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Dysfunctional T cell metabolism in the tumor microenvironment

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Abstract

Metabolic and signaling pathways are integrated to determine T cell fate and function. As stimulated T cells gain distinct effector functions, specific metabolic programs and demands are also adopted. These changes are essential for T cell effector function, and alterations or dysregulation of metabolic pathways can modulate T cell function. One physiological setting that impacts T cell metabolism is the tumor microenvironment. The metabolism of cancer cells themselves can limit nutrients and accumulate waste products. In addition to the expression of inhibitory ligands that directly modify T cell physiology, T cell metabolism may be strongly inhibited in the tumor microenvironment. This suppression of T cell metabolism may inhibit effector T cell activity while promoting suppressive regulatory T cells, and act as a barrier to effective immunotherapies. A thorough understanding of the effect of the tumor microenvironment on the immune system will support the continued improvement of immune based therapies for cancer patients.

Keywords

T-cell; Immunotherapy; Mitochondria; Glycolysis; Oxidative phosphorylation

1. Introduction

A longstanding goal in cancer therapy has been to enlist the immune system to eradicate tumors. Beyond virally-induced tumors, however, cancer vaccines have historically shown limited durable results [1]. It is now apparent that aspects of the tumor microenvironment both directly and indirectly impair immune cell functions [2]. Most notably, tumor cells and tumor-associated stromal cells express inhibitory immune checkpoint ligands that suppress T cell function. Therapeutic targeting of immune checkpoint inhibitors including programmed cell death protein 1 (PD-1) and its ligand (PD-L1), as well as monoclonal antibodies blocking cytotoxic lymphocyte antigen 4 (CTLA-4), are transforming the standard of care in both hematologic and solid tumor malignancies. Across multiple tumor types including

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melanoma, non-small cell lung cancer, and renal cell carcinoma, objective response rates average 20–30%, with many patients gaining durable benefit from these treatments [3-5]. In addition to the direct suppression of immunity through regulatory ligands, tumor cells also create a microenvironment that is metabolically hostile to effector lymphocytes. Tumors deplete nutrients and accumulate waste products, such as lactate or kynurenine, that directly inhibit T cells [6-9].

Control of T cell metabolism has become clearly defined as a key regulatory aspect of T cell function. Lack of nutrients causes cellular starvation, decreased proliferation, and inhibition of associated inflammatory effector function [10]; for example, glucose depletion or lactate accumulation impairs effector T cell function and secretion of Interferon-γ (IFNγ) [11-14], while kynurenine accumulation leads to the generation of immune suppressive regulatory T cells (Treg) [15]. Indeed, an inability of T cells to acquire sufficient glucose *in vivo* due to deficiency in the glucose transporter Glut1 prevents inflammatory responses [16]. Conversely, Tregulatory T cells (Treg) have been shown to be less dependent on glucose and more reliant on mitochondrial oxidative metabolism of lipids [17-19]. The availability of nutrients thus provides essential components and signals used in determining T cell fate and function. Growing evidence also indicates that modulation of T cell metabolic pathways contribute to the function of PD-1 and CTLA4. CTLA4 suppresses CD28-mediated T cell co-stimulation, which is essential for T cells to upregulate glucose uptake and metabolism [20,21]. Likewise, PD-1 signaling suppresses glucose metabolism in T cells and instead promotes lipid oxidation that is associated with reduced inflammatory T cell function [21,22]. Understanding the metabolic requirements for effector or regulatory T cell subsets during normal physiology may provide therapeutic opportunities to modulate the dysfunctional immune response in cancer and autoimmunity.

2. The physiology of T cell activation and T cell subsets

2.1. Differential metabolic dependencies of T cell subsets

In healthy cells, the most efficient metabolic pathway to generate energy is through mitochondrial dependent oxidative phosphorylation. The process of oxidative phosphorylation includes donation of electrons through the electron transport chain creates a proton and pH gradient across the mitochondrial membrane that is captured in the production of ATP, mediated via ATP synthase when protons return across this gradient [23]. The primary metabolic need of surveilling T cells prior to activation is maintenance basal cell physiology and motility. Resting naïve and memory T cells thus use oxidative phosphorylation as an efficient form of energy production for metabolic requirements (Fig. 1). T cell stimulation after encounter with antigen, interaction with co-stimulatory ligands and inflammatory cytokines, induces rapid T cell proliferation. To support new effector functions and biosynthetic demand, T cells undergo metabolic reprogramming that requires increased glucose uptake and glycolysis [10]. This transition is mediated in part through increased expression and cell surface trafficking of the glucose transporter, Glut1. Treg also increase glucose uptake and glycolysis, but are not Glut1 dependent [16]. Rather than promote Treg suppressive functions, increased glycolysis provides a negative feedback to reduce expression of the Treg transcription factor FoxP3 and impair suppression [24-27].

While elevated glycolysis provides only limited additional ATP, oxidative phosphorylation continues and the increased nutrient uptake supports anabolic metabolism, thus providing an abundance of biosynthetic intermediates for macro-molecular synthesis and cell growth.

2.2. Signaling cascades that control metabolic pathways alter T cell fate

There are several critical signaling mechanisms by which T cells induce metabolic reprogramming to support effector function. Hypoxia Inducible Factor a (HIF1α) responds to decreased oxygen availability to promote expression of glycolytic enzymes and mechanisms to decrease cellular reliance on mitochondrial oxidative metabolism. In addition to hypoxia-mediated regulation, HIF1α enhances glycolytic activity and formation of Th17 cells [28,29]. The classical pathways known to regulate metabolism of T cells include a balance between the activation of mammalian target of rapamycin (mTOR complex 1, mTORC1) and adenosine monophosphate-activated protein (AMPK) pathways. mTOR is a serine/threonine kinase that acts as the kinase component of mTORC1 to integrate multiple environmental cues, including signaling in T cells from the co-stimulatory receptors such as CD28, to control diverse cellular functions involved in growth, metabolism, ribosomal biogenesis, and autophagy [30]. The mTORC1 pathway is activated upstream by phosphoinositol-3-kinase (PI3K) to regulate cellular processes that determine cell fate of T cell subsets. mTORC1 is not activated solely downstream of PI3K but also senses and requires nutrient availability, including that of various amino acids. For example, mTORC1 is not activated in cells that are unable to uptake or access the branch chain essential amino acid leucine [31]. While T cells lacking mTOR kinase itself are unable to generate all effector T cell subsets and instead can produce only Treg, mTORC1 plays a specific role that is essential for Th1 and Th17 effector cells [32,33]. mTORC1 activation by PI3K upregulates the pentose phosphate pathway and glycolysis, in part through increased production of HIF1α [34]. AMPK can serve as the counter balance to mTOR signaling and serves to increase catabolic metabolism in response to metabolic stress [35]. Through direct kinase activity and inhibition of mTORC1 complex, AMPK can suppress glycolysis while upregulating oxidative metabolism and mitochondrial complex 1 activity [36]. AMPK activation can promote generation of Treg *in vivo* [37] and AMPKα1 is also necessary for the development of Th1 and Th17 development during acute infection, likely by mitigating metabolic stress [38].

While the switch from oxidative phosphorylation to a more glycolytic metabolic program is well described as a general property of effector T cells, it is now apparent that each T cell functional subset utilizes a distinct metabolic program. Indeed, Th1, Th17, and Treg are each metabolically distinct when examined by high-resolution metabolomics [25]. Th1 and Th17 rely heavily on high glycolytic capacity, while Treg oxidize lipids and do not require the glucose transporter Glut1 [18]. The specific metabolic requirements of each subset can be specifically demonstrated at the levels of Pyruvate Dehydrogenase (PDH) and Pyruvate Dehydrogenase Kinase (PDHK); PDHK phosphorylates and inhibits PDH to prevent conversion of pyruvate to acetyl-CoA for use in mitochondrial oxidative metabolism. Thus, inhibition of PDHK promotes PDH activity and oxidative metabolism. Indeed, inhibition of PDHK enhanced formation of Treg [25,39]. Effector T cells are differentially regulated by PDHK depending on expression of the kinase. While Th1 cells were not affected by PDHK

inhibitors, suggesting Th1 cells have a limited capacity for pyruvate oxidation or alternate modes of pyruvate regulation, Th17 cells were impaired and had reduced IL17 production upon PDHK inhibition [25]. Similar nuances in T cell subset specification can be seen by pharmacologic inhibition or knockdown of acetyl-CoA carboxylase that blocks de novo fatty acid synthesis and decreases both glycolysis and tricarboxylic acid cycle. This treatment resulted in decreased formation of Th17 and increased development of Treg [40].

2.3. The role of cytokines in T cell metabolism and subset specification

Distinct cytokine expression patterns drive the specification of T cells into functional subsets and play important roles to shape T cell metabolic programs [41]. In fact lymphocytes without extrinsic cytokine signals are unable to maintain basal metabolic pathways and viability [42]. Stimulation by cytokines such as IL-7, IL-15, IL-2, and IL-4 have been shown to regulate T cell metabolism and viability [42]. IL7R expression is essential for resting T cells to maintain glucose uptake and glycolysis in vivo [43] and IL-2 and IL-15 can play critical roles in the metabolism of activated T cells [8]. Following cytokine stimulation, activation of Janus kinases (JAK) leads to phosphorylation and activation of STAT transcription factors that can directly regulate cellular metabolism. STAT1, which can be activated by stimulation with IFNγ, may promote expression of glycolytic genes to promote the metabolism characteristic of Th1 cells [44]. STAT3 activation by IL6 also has an alternate metabolic role and translocates to mitochondria to promote PDH activity and pyruvate metabolism that can support electron transport and oxidative phosphorylation [45,46]. Similarly, cytokines that drive specification of T cells into distinct subsets do so in part through regulation of lineage-related transcription factors that can guide specific T cell metabolic programs. Th17 cells are characterized by expression of RORγt, which has been shown to associate with the Hypoxia Inducible Factor-α (HIF1α) and induce glycolytic genes [19,29]. Bcl6 promotes follicular helper T cells (Tfh) and may also regulate T cell metabolism, but instead of activating glycolysis, Bcl6 suppresses expression of glycolytic genes [47]. In addition, Treg associated FoxP3 can also suppress glycolysis and promote mitochondrial oxidative pathways [48-50].

Metabolic pathways can, in turn, directly modulate inflammatory cytokine expression. IFNγ is produced primarily by natural killer, CD4 T helper, and cytotoxic CD8 effector cells and provides direct feedback to regulate T cell homeostasis and promote Th1 and CD8 T cell inflammation. Glucose limitation has a selective effect to reduce IFNγ expression, while IL2 production is far less sensitive to glucose levels [11,51,52]. Mechanistically, this may occur in part through regulation of IFNγ protein translation. The glycolytic enzyme GAPDH has been shown to bind the 3′UTR of IFNγ mRNA to reduce translation if levels of the glycolytic intermediate and GAPDH substrate glyceraldehyde-3-phosphate decrease [12]. In addition to metabolic regulation of IFNγ at the translational level, lactate dehydrogenase A is induced during aerobic glycolysis and plays a key role to maintain acetyl-CoA levels that support acetylation of histones at the *ifng* locus to promote IFNγ expression [14]. Cytokine signaling also can act together with metabolic pathways to determine cell fate. Cytokine-induced Th1 development was most prominent in high glucose conditions, whereas Th17 cells were preferentially generated in an aromatic amino acid rich environment [53].

3. The tumor microenvironment and T cell function

3.1. Limiting resources tumor microenvironment alter T cell metabolism

It is becoming evident that the dependence of T cell activation and effector functions on metabolic reprogramming to increase glucose and amino acid uptake and metabolism can restrict T cell function in nutrient-limiting environments. Tumors may impede T cell access to nutrients and thus impair T cell metabolism and function through multiple means (Fig. 2). Similar to effector T cells, tumor cells frequently use aerobic glycolysis which, when combined with limited vascular exchange due to poor angiogene-sis, may lead to depletion of key nutrients [54]. Indeed, glucose levels have been found to be significantly reduced in some tumors [7,55,56], although heterogeneity in tumor microenvironments may lead to selective regions of tumors that are replete or deficient with glucose. In principle, this restriction of nutrients may result in competition between T cells and tumor cells for limiting glucose or amino acids. Rapidly dividing tumors that consume glucose necessary for T cell activation may thus promote AMPK signaling that inhibits effector T cell subsets by suppressing mTORC1 activity. The selective requirement of effector T cells for glucose, while Treg are less glucose-dependent, would thus favor Treg over effector T cells in the glucose-limited tumor microenvironment. Amino acids may in principle also be depleted similar to glucose, and the dependence of effector T cells on abundant amino acids could further restrict anti-tumor responses. T cells deficient in glutamine and neutral amino acid transporters fail to generate effectors and are protected from inflammatory diseases [57,58].

Likewise, mechanisms that actively deplete arginine or tryptophan by Argininase or Indoleamine 2,3-Dioxygenase (IDO1), respectively, are immune suppressive. Arginine deficiency inhibits T cell activation through insufficient polyamine production and through the ability of arginine to directly bind key transcription factors in a second-messenger-like regulatory mechanism [59,60]. Trypto-phan deficiency is also immunosuppressive and appears to act indirectly through a failure to load tRNA with tryptophan and an accumulation of uncharged tRNA that promote a GCN2-mediated unfolded protein response that impairs proliferation and leads to immunosuppressive IL10 and TGFβ production [61].

3.2. Waste products produced by tumor cells change effector T cell function

In addition to consumption of key nutrients, tumor cells produce metabolic waste and signaling products that can impair T cell metabolism and function. Lactate can accumulate high levels in tumors due to the use of aerobic glycolysis by cancer cells and can directly modulate T cells [55]. The migration of T cells has been shown to be impaired by lactate and lactic acid, which can alter T cell expression of chemokine receptors [62]. Accumulation of lactate also impairs T cell signaling through Nuclear Factor of Activated T cells (NFAT) and leads to reduced IFNγ and Lactate Dehydrogenase expression. In mouse models, lactate levels negatively correlates with markers of T cell activation in melanoma [6].

IDO is involved in the degradation of tryptophan to kynurenine and was found to be upregulated in many tumors, leading to suppression of IFNγ production [63]. IDO both depletes tryptophan and produces the immune modulatory metabolite kynurenine. Increased levels of kynurenine in the tumor microenvironment leads to increased Treg subset activity

and inhibition of effector T cells [64]. Kynurenine is an endogenous ligand for the Aryl Hydrocarbon Receptor (AHR) [65], which is best understood as a xenobiotic receptor and shown to have generally immune suppressive activities while also promoting generation of Treg [66].

Tumor cells also generate high levels of extracellular adenosine that can promote immune evasion. ATP is released by dying cells and can be pro-inflammatory. Extracellular ATP accumulates in tumors and can signal through purinergic P2X receptors on T cells. Similar to other “danger” patterns, extracellular ATP signals tissue damage and can promote inflammation [67]. However, tumors often upregulate ectoenzymes, CD39 and CD73, that promote the metabolism of extracellular ATP to AMP then adenosine. In contrast to extracellular ATP, adenosine is immunosuppressive through activation of the Adenosine Receptor (A2R). Indeed, tumors with high levels of CD73 have been shown to have a poor prognosis [68] and preclinical models suggest that the combined inhibition of this negative regulatory signal CD73 along with PD-1 blockade limits tumor growth [69]. IDO and A2 receptors are currently being investigated as therapeutic targets for antitumor therapy alone and in combination with checkpoint inhibition. Indoximod, an IDO inhibitor, has been used in phase I trial with docetaxel for patients with metastatic solid tumors where it was found to be well tolerated and without significant toxicity [70].

3.3. Cell signaling pathways affected in the tumor microenvironment

Cancer cell-mediated inhibition of T cell signaling and metabolism can impair T cell activation and anti-tumor responses. Even in hematopoietic cancers, B cell leukemia can lead to a broad suppression of T cells that impairs T cell mTORC1 signaling and glycolysis [71]. Importantly, genetic rescue of Akt/mTORC1 signaling or glucose uptake could partially restore T cell function and slow leukemia progression in an animal model [71]. Chronic stimulation of CD8 T cells in the tumor microenvironment leads to expression of inhibitory markers CTLA-4 and PD-1 that negatively regulate T cell activation, metabolism, and function. While both act to suppress mTORC1 signaling, PD-1 directly inhibits PI3K signaling, while CTLA-4 phosphorylates PP2A, thus inhibiting T cell activation through AKT. These separate methods of regulation indicate independent and potentially synergistic pathways to regulate T cell activation [21]. Both CTLA4 and PD-1, however, modulate T cell metabolism by decreasing Glut1, glycolysis, and promoting lipid oxidation to restrict the metabolic program essential for effector T cells [20-22,72]. PD-1 blockade has been shown to activate specific subsets of CD8 T cells based on levels of PD-1 expression [73]. A better understanding of the specific CD8 T cell subset and signaling pathways activated following checkpoint inhibition may allow for improved patient selection to receive these costly therapeutics. For example, selective inhibition of PI3Kδ, decreased AKT activation and phosphorylation of phospho-S6 in Treg cells *in vitro*, thus decreasing cell proliferation and survival while not altering effector CD4 T cells or CD8 T cells. Selective inhibition of PI3Kδ similarly decreased CD4 Treg in tumor models, while increasing CD8 vaccine induced T cells, resulting in a synergistic enhancement of tumor suppression [74].

Similar to expression and activity of inhibitory regulators, changes in metabolites and metabolic enzymes have been shown to directly control T cell effector function. In addition

to the potential depletion of glucose in the tumor microenvironment, subsequent limitation of biosynthesis and ATP production, as well as exhaustion of the glycolytic metabolite phosphoenolpyruvate (PEP), negatively affects antigen receptor signaling. Glycolytic flux and PEP were shown to enhance calcium signaling upon T cell activation and promote effector functions of CD4 and CD8 T cells such that increased PEP generation promotes anti-tumor immunity and prolongs survival in a melanoma mouse model [7]. GAPDH can also play a key regulatory role for T cells [12]. The localization of GAPDH is controlled in part by access to glyceraldhyde-3-phosphate (G3P). In limiting glucose, G3P cannot be produced through glycolysis by GAPDH, and GAPDH localizes to polysomes and the 3′UTR of IFNγ in a manner that can suppress translation. G3P control of GAPDH may be critical for this regulatory mechanism as provision of G3P was sufficient to increase IFNγ expression even in the presence of galactose, a substrate that promotes oxidative phosphorylation [12]. In addition, AMP accumulation in cells under metabolic stress leads to AMPK activation and suppression of mTORC1 activity, glycolysis, and T cell effector function [75].

4. Dysfunctional mitochondria in the tumor microenvironment

Mitochondria possess many important cellular functions, including the capacity for oxidative phosphorylation coupled with the electron transport, regulation of reactive oxygen species, localization of pro-apoptotic proteins, and inner membrane polarization for ATP synthase. Mitochondria maintain each of these functions through a balance of biogenesis, degradation, and highly dynamic fission and fusion events that depend on the environment and needs of the cell. Mitochondrial mass and quality control are dependent on the fluent biosynthesis and autophagic degradation known as mitophagy that degrades dysfunctional or damaged mitochondria [76]. T cells must closely regulate mitochondrial numbers and function to allow the metabolic transition of oxidative naïve T cells to glycolytic T cell effector states. *In vitro* studies and mouse models have demonstrated that punctate mitochondria are commonly found in effector T cells and that alteration of cristae morphology by the inner membrane protein Opa1 and fusion in memory-like T cells favors their oxidative phosphorylation [77]. During lymphocyte proliferation and renewal, the elimination of mitochondria through mitophagy also plays an important role in determining lymphocyte differentiation vs self-renewal [78] and autophagy-deficient T cells fail to efficiently generate memory [79-81]. Further, memory T cells are metabolically primed and have higher mitochondrial mass and levels of ATP with increased oxidative phosphorylation and glycolytic capacity upon stimulation than stimulated naïve cells [82,83].

Chronically-stimulated lymphocytes have altered mitochondria that may contribute to poor function. Chronic viral infection leads to accumulation of exhausted T cells with dysfunctional mitochondria that exhibit higher levels of reactive oxygen species [84]. Mitochondrial mass is dependent on the fluent biosynthesis and autophagic degradation known as mitophagy that degrades dysfunctional or damaged mitochondria [76]. In the setting of chronic stimulation in the tumor microenvironment, T cell can become deficient for mitochondrial numbers or function [85]. This loss of mitochondrial quality control may be due to decreased expression of the transcription coactivator peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1α), a master regulator of genes

involved in mitochondrial biogenesis [86]. PGC-1α is activated in response to hypothermia, ROS, and a multitude of other signals where alongside transcription factors it regulates genes involved in fatty acid oxidation, glucose utilization, and mitochondrial proteins. In chronic stimulation following viral infection, PGC-1α was negatively regulated by PD-1 signaling [84]. In this model, expression of PGC-1α increased glucose uptake and mitochondrial membrane potential. Similarly, in a B16 melanoma model, expression of PGC-1α in T cells enhanced T cell activity and led to prolonged survival, suggesting that failed mitochondrial quality control prevents anti-tumor immunity [85].

These data demonstrate that chronically stimulated T cells may be functionally rescued by improvement in the structure and function of their mitochondria. To further support this notion, transcriptional analysis of lymph nodes in PD-1 deficient mice showed upregulation of mitochondrial genes, and tumor responsive CD8 T cells exhibited higher ROS, larger mitochondrial mass, and higher levels of mitochondrial membrane potential [87]. Augmentation of mitochondrial ROS using electron transport chain (ETC) uncouplers showed enhanced tumor killing in combination with PD-1 blockade. The ETC uncouplers activated mTOR and AMPK pathways. Combination of PD-1 blockade with mTOR or AMPK activation similarly provided synergistic effect prolonging survival compared to PD-1 blockade alone [87]. Similarly, viral models of chronic stimulation using hepatitis B virus (HBV) demonstrate extensive changes in CD8 mitochondria, including elevated levels of mROS; treatment with mitochondrial targeted antioxidants was shown to rescue HBV specific T cell effector function [88].

5. Outlook on metabolic barriers to T cell function in cancer

Immunotherapy now offers new promise to treat a growing range of tumors. However, the complexity of the metabolic regulation of T cell subsets and the influence of the tumor microenvironment may have significant implications for the effectiveness of these therapies. In adoptive T cell therapy with chimeric antigen receptors, the co-stimulation and metabolic status of the T cell can have a significant effect on anti-tumor immunity. Targeting metabolic pathways by using the 4-1BB co-signaling receptor to augment respiratory capacity, fatty acid oxidation, and mitochondrial biogenesis vs the CD28 receptor that comparatively enhanced glycolysis, may enable creation of CAR T cells with enhanced survival and long-term function [89]. Similarly, restoration of T cell metabolism in mice bearing B cell leukemia led to increased T cell activation and anti-tumor function, demonstrating that inhibition of T cell metabolism contributes to poor anti-tumor immunity even in liquid tumors [71]. In solid tumors where the tumor microenvironment and nutrients available to T cells may be significantly altered, phase I trials are ongoing to determine safety and efficacy of IDO inhibitors in combination with checkpoint inhibitors (clinicaltrials.gov). When checkpoint inhibition does demonstrate efficacy for patients, many questions remain: which subset of T cells are active; which metabolic pathways are upregulated; what predicts response for patients to checkpoint inhibition. It is an exciting time to delve into these problems and questions to learn how metabolic regulation of T cells impacts checkpoint inhibitor therapy.

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Biographies

Kathryn Beckermann received both her M.D. and Ph.D in biochemistry at Vanderbilt University Medical Center in Nashville, TN. Her dissertation work focused on identification of novel p53 target genes and characterization of one of these in a *p53* dependent mechanism of cell death through autophagy. She is now completing her hematology/oncology fellowship performing research focused on the metabolic implications in the tumor microenvironment and how these may affect immunotherapy in patients with cancer.

Stephanie Dudzinski studies cancer immunoengineering for her Ph.D. work in the laboratories of Dr. Jeffrey Rathmell and Dr. Todd Giorgio. She received her bachelor of science in engineering from Duke University before joining Vanderbilt's Medical Scientist Training Program.

Jeffrey C. Rathmell Director, Vanderbilt Center for Immunobiology, Cornelius Vanderbilt Professor of Immunobiology, Department of Pathology, Microbiology, and Immunology, Cancer Biology. Dr. Rathmell studies mechanisms that influence lymphocyte death and differentiation in inflammatory diseases and cancer. Following undergraduate studies at the University of Northern Iowa, his earned a PhD in Immunology at Stanford University. In postdoctoral studies at the University of Chicago and University of Pennsylvania, he showed that lymphocyte metabolism was dynamically regulated to control cell function and survival in inflammatory diseases and cancer. He began at Duke University in 2003 in the departments of Pharmacology and Cancer Biology and Immunology and moved in 2015 to Vanderbilt University to direct the Vanderbilt Center for Immunobiology and co-leads to Host Tumor Interactions Program of the Vanderbilt Ingram Cancer Center. The ongoing focus on Dr. Rathmell's ongoing work is to understand how metabolic pathways regulate CD4 T cell subsets in inflammatory diseases and how the tumor microenvironment and metabolism impacts anti-cancer responses.

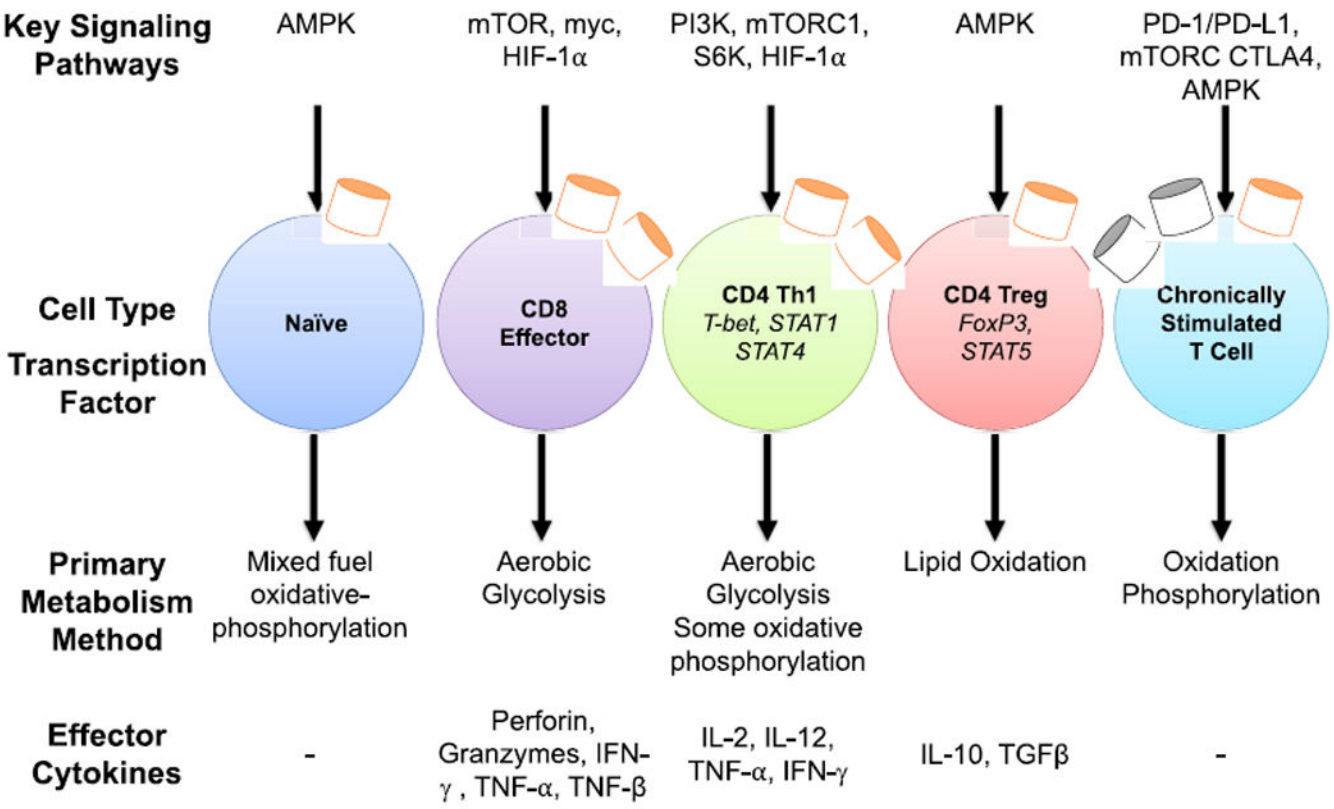

Fig.1.

The metabolic programs of T cell subsets. Distinct T cell subsets utilize specific metabolic programs to support their functions. Each functional subset is characterized by signaling pathways, transcription factors, metabolic programs, and effector cytokines.

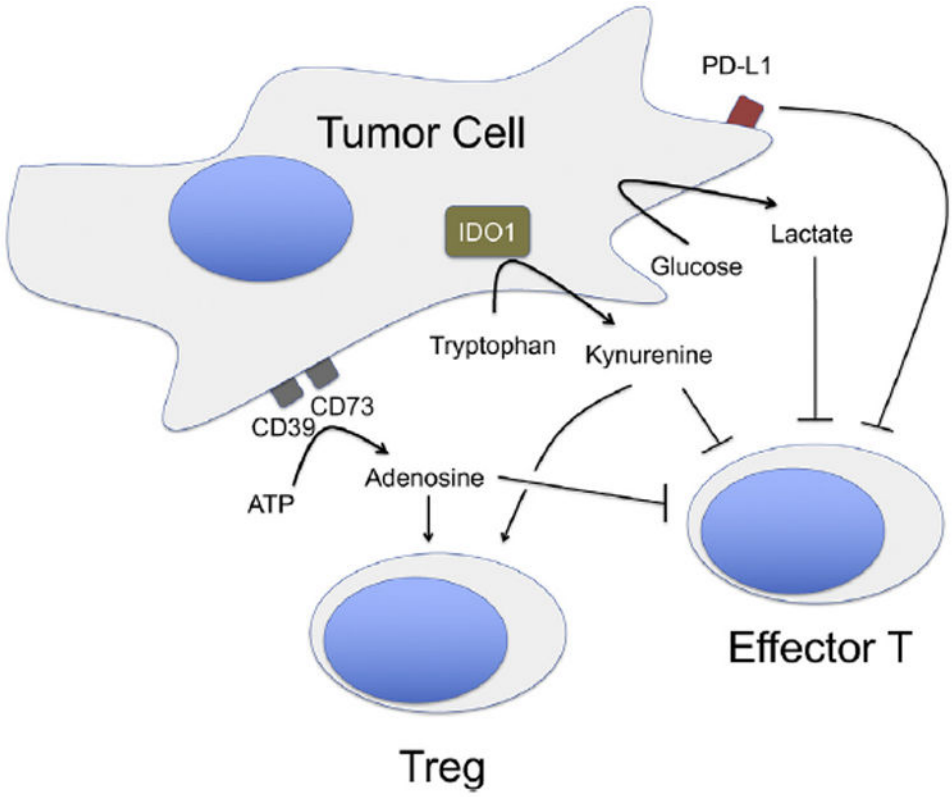

Fig. 2.

Tumor cells inhibit effector T cell metabolism and function through multiple means. Tumor cells express CD39 and CD73 that can produce adenosine from extracellular ATP and IDO1 that can both deplete tryptophan and produce kynurenine. The metabolism of tumor cells also consumes glucose and can lead to lactate accumulation, both of which can suppress effector T cells and promote Treg. PD-1 can also influence T cell metabolism to suppress glycolysis and promote oxidative metabolism.