Review

CellPress

Special Issue: Immunity and Cancer

T cell metabolic fitness in antitumor immunity

Peter J. Siska and Jeffrey C. Rathmell

Department of Pharmacology and Cancer Biology, Department of Immunology, Duke Molecular Physiology Institute, Duke University, Durham, NC 27710, USA

T cell metabolism has a central role in supporting and shaping immune responses and may have a key role in antitumor immunity. T cell metabolism is normally held under tight regulation in an immune response of glycolysis to promote effector T cell expansion and function. However, tumors may deplete nutrients, generate toxic products, or stimulate conserved negative feedback mechanisms, such as through Programmed Cell Death 1 (PD-1), to impair effector T cell nutrient uptake and metabolic fitness. In addition, regulatory T cells are favored in low glucose conditions and may inhibit antitumor immune responses. Here, we review how the tumor microenvironment modifies metabolic and functional pathways in T cells and how these changes may uncover new targets and challenges for cancer immunotherapy and treatment.

Introduction

The ability of the adaptive immune system to eliminate invading pathogens has long suggested that T cells have the capacity to respond to neoantigens or inflammatory and damage signals to eliminate tumors [1]. However, tumor microenvironments can pose particular challenges for antitumor T cell responses. It was first recognized during the early 1920s that tumors utilize glucose at a high rate and produce lactate in a process termed the 'Warburg effect' [2]. This metabolic program differs from that used by most normal tissues in that nutrients such as glucose are not readily oxidized in mitochondria for maximal ATP generation, but are instead conserved for biosynthesis of nucleic acids, lipids, and amino acids to support cell growth [3]. While a key benefit of this metabolic program is to protect tumor cells in hypoxic regions, oncogenes that drive this mode of metabolism do so even in the presence of oxygen in a metabolic program termed 'aerobic glycolysis'. Cancer cells utilize aerobic glycolysis to differing extents, and high levels of glycolytic activity coupled with poor angiogenesis can lead to near glucose depletion and accumulation of waste products, such as up to 20 or more millimolar levels of lactate in both vital and perinecrotic tumor zones [4]. Thus, T cells infiltrating the tumor microenvironment face significant metabolic challenges to mount and sustain an antitumor response.

Despite these barriers, approaches to interfere with inhibitory immunomodulatory signals in immune checkpoint therapies have shown that tumor-infiltrating CD4 and CD8 T cells can have key roles in the control or mediation of antitumor immunity [5]. Specifically, inhibition of Cytotoxic T Lymphocyte-Associated Protein 4 (CTLA4) and PD-1 interactions with ligands have enhanced antitumor responses that can lead to curative therapy in some cancers, most successfully in melanoma [5]. These findings suggest that, at least in some cases, T cell-mediated antitumor responses are initiated even in potentially nutrient-limited tumor microenvironment conditions, but are held in check by immunosuppressive mechanisms. It is now widely appreciated that T cell differentiation and effector function are coupled to metabolic reprogramming processes, and that interfering with these reprogramming pathways can impair T cell responses [6]. This has suggested that tumor-mediated immune suppression is associated with alterations to the metabolic pathways that would normally support T cell effector function. Here, we review evidence in support of this notion, and propose that T cell 'metabolic fitness' is central to effective antitumor immunity, and is modulated by both the tumor nutrient microenvironment and immune checkpoints.

Metabolic reprogramming in T cell differentiation and effector function

To exert function, activated T cells must undergo metabolic reprogramming to shift from an energy-oriented oxidative metabolism that supports quiescence and immune surveillance, to a primarily anabolic and biosynthetic metabolism to support rapid growth. After pathogen clearance, T cells are eliminated in clonal contraction or return to a primarily catabolic metabolism as long-lived memory cells [6]. Naïve T cells are small and quiescent cells that require relatively small amounts of glucose, amino acids, and fatty acids to maintain basic energetic and minimal replacement biosynthesis demands. Encounter with cognate antigen in the context of appropriate costimulation triggers T cell activation and differentiation into effector T cells (Teff cells), which reduce lipid oxidation and instead rely on a high intake of glucose and amino acids [7] to support

Corresponding author: Rathmell, J.C. (Jeff.rathmell@duke.edu).

Keywords: T cell metabolism; glycolysis; IDO; PD-1; CTLA4; tumor microenvironment; antitumor immunity; checkpoint blockade.

1471-4906/

 http://dx.doi.org/10.1016/j.it.2015.02.007

proliferation and effector functions, such as cytotoxicity and cytokine production. The pathways that control these metabolic transitions are now beginning to be unraveled. The T cell receptor (TCR) with CD28 costimulation activates the Phosphatidylinositide 3 Kinase (PI3K)/Akt/Mammalian Target of Rapamycin (mTOR), cMyc, and Hypoxia Inducible Factor (HIF1α) signaling pathways, which promote glycolytic gene expression and post-translational regulation, which are essential to induce aerobic glycolysis and amino acid metabolism of Teff cells [8–11] (Figure 1). In particular, activated effector T cells sharply increase glycolysis and glutamine metabolism to support anabolic pathways of nucleotide and lipid synthesis that are essential for cell growth [6,7,11,12]. Inhibition of glucose or glutamine metabolic enzymes can reduce Teff cell activation and function, because glucose deprivation or treatment with inhibitors of glycolysis can impair Teff cell proliferation and cytokine secretion [11,13–15]. Indeed, inhibitors of nucleotide synthesis are potent immunosuppressive agents that are standard of care for a variety of rheumatologic diseases [16].

Thus, the inability to gain access to appropriate nutrients poses a significant barrier to Teff cell function. To avoid this potential limitation, T cell activation leads to upregulation of both glucose and amino acid transporters [17–19], and regulation of nutrient uptake is now appreciated to be a critical component of T cell activation and function. Indeed, genetic disruption of amino acid uptake through the transporters solute carrier family 7 (amino acid transporter light chain, L system), member 5 (SLC7a5) or SLC1a5 impairs growth and proliferation of Teff cells [18,19]. Likewise, T cells express a panel of glucose transporters and genetic deletion of the glucose transporter Glut1 (SLC2a1) sharply reduced T cell glycolysis and proliferation *in vivo*, preventing CD4 T cells from inducing multiple inflammatory diseases, including mouse models of graft versus host disease after allogeneic bone marrow transplant and colitis [15]. This was also true in peripheral human CD4 T cells, where reduction in Glut1 expression by siRNA impaired T cell growth and proliferation after activation [15]. Further supporting the notion

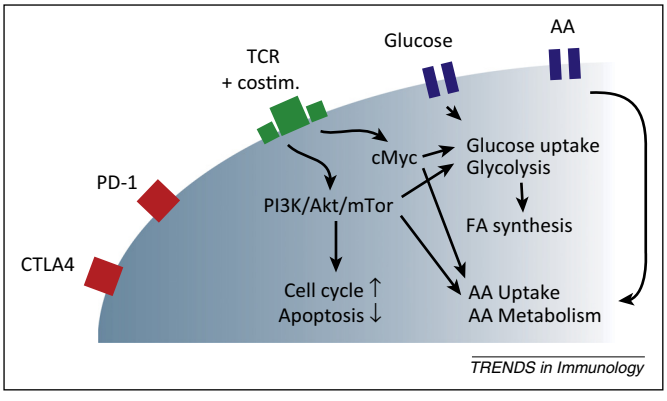

Figure 1. Metabolic regulation and feedback in T cell immunity. T cell activation and signaling through T cell receptor (TCR) activates Phosphatidylinositide 3 Kinase (PI3K)/Akt/Mammalian Target of Rapamycin (mTOR) and cMyc pathways, leading to increased glycolysis and metabolism in effector T cells (Teff cells). Abbreviations: AA, amino acids; FA, fatty acids; CTLA4, Cytotoxic T Lymphocyte-Associated Protein 4; Costim, costimulation; PD-1, Programmed Cell Death 1.

that glucose uptake modulates T cell physiology after activation, transgenic overexpression of Glut1 to increase glucose uptake in T cells was sufficient to augment T cell stimulation by enhancing proliferation and inflammatory cytokine production upon submitogenic stimulation [17]. Ultimately, this increased T cell activation led to lymphadenopathy and a systemic lupus erythematosus-like autoimmunity as the mice aged [17,20].

After activation, T cells can differentiate into functional Teff cell and regulatory T cell (Treg cell) subsets that may have critical and differential roles in the control of tumors. These subsets have now been shown to utilize and require distinct metabolic programs [6,21]. While Teff cells are key drivers of antitumor immunity, Treg cells can inhibit Teff cells to suppress immunity [22] and are generally associated with poor prognosis in many cancers [23–26]. An exception is colorectal carcinoma, where Treg cells have been reported in some cases to be associated with better patient outcome [27]. This discrepancy may be due to a role of inflammation in the promotion of the development and progression of colorectal carcinoma that Treg cells could suppress [28]. Metabolically, while activated CD8 T cells and CD4 Teff cells require high levels of Glut1 and glucose metabolism, Treg cells express low levels of Glut1 and can be Glut1 independent and not reliant on high rates of glucose metabolism [10,15,20]. Treg cells are instead primarily oxidative and can efficiently metabolize pyruvate through the tricarboxylic acid cycle (TCA) or utilize lipid beta-oxidation as a primary metabolic mechanism [10,15,20]. Also unlike Teff cells, Treg cells do not require the mTOR kinase and are preferentially generated when T cells are deficient in mTOR kinase or if mTOR complex 1 (mTORC1) is inhibited by rapamycin [29]. Opposing mTORC1 is the AMP-activated Protein Kinase (AMPK), which is activated in conditions where nutrients are limiting and promotes oxidative metabolism [30]. AMPK can be highly phosphorylated and activated in Treg cells [20] and activation of AMPK by treatment with metformin can decrease Teff cell and increase Treg cell frequency *in vivo* [20,31]. Therefore, conditions in the tumor microenvironment that restrict Teff cell nutrient uptake and metabolism may alter mTORC1 and AMPK signaling to impair Teff cells or induce Treg cells that may then suppress antitumor immunity [23–25]. Conversely, interventions that improve the ability of Teff cells to compete with tumor cells for the uptake of essential nutrients may increase the metabolic fitness of T cells to improve the functional capacity of Teff cells to mediate an antitumor immune response.

Glucose metabolism and nutrient microenvironment limit antitumor immunity

The abundance of glucose is critical for activated T cells and the potential depletion of glucose in tumors [4] may promote competition for nutrients and suppress Teff cell function. Metabolic stress with insufficient glucose can greatly alter T cell signaling and gene expression. Culture of T cells in glucose-limiting conditions has been shown to inhibit signaling through the mTORC1 pathway to reduce phospho-S6 and lower expression of up to one-tenth of antigen-induced genes to impair cell adhesion, cell cycle