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T cell metabolic reprogramming and plasticity

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Abstract

Upon antigen stimulation, small and quiescent naïve T cells undergo an approximately 24hr growth phase followed by rapid proliferation. Depending on the nature of the antigen and cytokine milieu, these proliferating T cells differentiate into distinctive functional subgroups that are essential for appropriate immune defense and regulation. T cells undergo a characteristic metabolic rewiring that fulfills the dramatically increased bioenergetic and biosynthetic demands during the transition between resting, activation and differentiation. Beyond this, T cells are distributed throughout the body and are able to function in a wide range of physio-pathological environments, including some with a dramatic metabolic derangement. As such, T cells must quickly respond to and adapt to fluctuations in environmental nutrient levels. We consider such responsiveness and adaptation in terms of metabolic plasticity, that is, an evolutionarily selected process which allows T cells to illicit robust immune functions in response to either a continuous or disrupted nutrient supply. In this review, we illustrate the relevant metabolic pathways in T cells and discuss the ability of T cells to change their metabolic substrates in response to changes in the environment.

Keywords

T lymphocytes; metabolism; reprogramming; plasticity

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Introduction

The reproduction and spreading of invading pathogens in vertebrates is often an extremely rapid process, resulting in acute and severe damage to the host. As such, an effective host-mediated immune response has to be fast and is energy intensive. The evolution of the vertebrate's T cell-mediated immunity has culminated in an effective and complex response, allowing T cells to recognize foreign antigen and rapidly engage a network of signaling processes. These processes are essential in order to support the following: cell growth, proliferation and differentiation. Recent emerging evidence has revealed that there is a coordinated rewiring of the cellular metabolic program following T cell activation. Beyond supporting immediate cell size growth and clonal expansion following activation, this metabolic rewiring is also critical for T cell lineage polarization, acquisition of effector function, and eventually the engagement of T memory programs. In this review, we will update our current understanding of T cell metabolic reprogramming; discuss the signaling mechanisms that regulate metabolic reprogramming; and discuss the alternative metabolic substrates and routes that are likely required for supporting T cell function.

T cell metabolic reprogramming

As an essential component of adaptive immunity, T cells recognize foreign antigen and rapidly transition from a quiescent to an active state that is concomitant with cell growth (increase in cell size) and proliferation. In addition, activated and proliferating T cells can differentiate into various functional subsets, largely determined by the nature of antigen stimulation and the surrounding cytokine milieu; in concert with downstream signaling, metabolic rewiring, and initiation of transcription factors. This transition results in a heterogeneous T cell subset population. Activated and differentiated T cells can engage a variety of metabolic pathways including upregulation of glycolysis, glutaminolysis, and fatty acid metabolism [1–10]. Nevertheless, each subset of T cells demonstrates unique metabolic demands that contribute to subset proliferation, differentiation, effector functions, and maintenance. Following the peak of T cell expansion and antigen clearance, the vast majority of T cells undergo programmed cell death (apoptosis) during a contraction phase. The remaining population returns to a quiescent state and gives rise to the memory subset, which responds more quickly and effectively upon subsequent encounter with the same pathogen. To fulfill their bioenergetic and biosynthetic demands, coupled with various functional stages, T cells actively engage distinct signaling pathways and transcriptional modulators to alter their metabolic programs as demonstrated in Figure 1.

During the rapid T cell growth and proliferation process, and as a result of activation signals, T cells reprogram their metabolic profile, shifting from fatty acid oxidation (FAO) to robust aerobic glycolysis, pentose phosphate pathway (PPP) and glutaminolysis. Naïve T cells rely on oxidative phosphorylation (OXPHOS), to generate energy in order to meet the basic needs of cellular function and survival. Heightened aerobic glycolysis and glutaminolysis in activated T cells not only support ATP generation, but also provide biosynthetic intermediates that are subsequently used as building blocks for amino acids, nucleotides, and lipids. Also, glutaminolysis and glycolysis in active T cells provide carbon and nitrogen for other growth and proliferation-associated biosynthetic pathways, such as hexosamine and

polyamine biosynthesis. The shunting of glucose into the PPP pathway results in the production of R5P and NADPH. While R5P is a precursor for ribonucleotides biosynthesis, NADPH determines cellular redox balance and coordinates with free fatty acid and cholesterol biosynthesis through providing reducing equivalents [2, 3, 11,12].

The rewiring of metabolic pathways upon T-cell activation is regulated by several signaling pathways, including mitogen activated protein kinase (MAPK)/extra-cellular signal-regulated kinase (ERK) and the PI3K/Akt/mTOR cascades, which varies depending on the T cell subset [2,13]. The activation of Akt signaling promotes the expression and cell surface trafficking of the glucose transporter-1 (Glut-1), facilitating glucose uptake [1, 6]. On the other hand, ERK signaling promotes glutamine uptake via modulating Sodium-dependent neutral amino acid transporter-2 (SNAT2) expression and cell membrane trafficking [15]. Beyond the regulation on glucose and glutamine uptake, T cell activation signaling drives a global metabolo-transcriptome including most of the key metabolic enzymes involved in major catabolic and biosynthetic pathways, with an example of this being the discovery that the proto-oncogene Myc is required in T cell activation driven glucose and glutamine catabolism [2, 13]. Upregulation of metabolic genes involved in lipid metabolism and *de novo* cholesterol biosynthesis and transport are under the dynamic control of transcription factors, nuclear receptor LXR, and the orphan steroid receptor ERR α [5, 17, 18].

Following a rapid initial growth phase, T cells enter a proliferation phase and subsequently differentiate into various phenotypic and functional subtypes. In response to distinct antigen challenge and extracellular cytokine signals, activated CD4⁺ T cells differentiate into immune suppressive regulatory T (T_{reg}) cells or inflammatory T effector cells, such as T helper T_H1, T_H2, T_H17 and follicular helper T (T_{fh}), each of which may engage characteristic metabolic programs. Accumulating evidences suggest that T_H1, T_H2 and T_H17 cells all sustain heightened glycolysis, while T_{reg} cells show enhanced FAO [5, 16, 19]. The metabolic pathways that are preferentially engaged in T_{fh} remain to be defined. Consistent with the metabolic preference of T_{eff} and T_{reg} cells, the supplementation of exogenous fatty acid inhibits T_H1, T_H2 and T_H17 differentiation, while modestly enhances T_{reg} differentiation [5]. In addition, T_{reg} differentiation is preferentially induced by the commensal microbe-derived short-chain fatty acid, butyrate; however, this effect may be attributed to the inhibition of histone deacetylase activity by butyrate [20,21]. Glucose has a major effect on T cell differentiation as evidenced by the fact that the blockade of glucose catabolism significantly inhibits T_{eff} function *in vitro* and *in vivo* [5, 16, 22]. This effect is likely due to the inhibition of glycolysis and mitochondrial-dependent oxidative phosphorylation. As the key biosynthetic and bioenergetic organelle, mitochondria are hubs of catabolic and anabolic pathways, which enable them to fulfill the various metabolic demands of immune cells ranging from generating ATP to providing precursors for macromolecule synthesis and ROS [23]. AMP-activated Protein Kinase (AMPK) is an important player in regulating mitochondrial-dependent oxidative metabolism. Recent evidence shows their immune phenotype. While genetic ablation of AMPK abolishes T_H1 and T_H17 development and their response to infection, the activation of AMPK by treatment with metformin can inhibit T_{eff} cell function and promote T_{reg} cell function *in vivo* [19, 24, 25]. A recent study has shown that the combination of targeting mitochondrial metabolism

and glycolysis through the AMPK activator, Metformin, and the hexokinase inhibitor, 2-deoxy-d-glucose (2DG), may significantly alleviate disease phenotypes in several systemic lupus erythematosus (SLE) mouse models. These results suggest that both mitochondrial metabolism and glycolysis are required to support CD4⁺ T cell effector function in SLE [26].

In addition to AMPK, HIF1 α has also been implicated in driving T_H17 differentiation and sustaining elevated glycolysis during this process [29–31]. T_H17 cell differentiation is driven by TGF- β and the proinflammatory cytokines IL-6, IL-21, and IL-23, which induce the transcription factor RAR-related orphan receptor gamma (ROR γ) and activate STAT3 [29]. Recent studies have demonstrated that activation of STAT3 leads to increased expression of HIF1 α [5,29, 30]. Consistent with the crucial role of mTORC1 in regulating T effector development and metabolism, the expression of HIF1 α is also dependent on the function of mTORC1 during T_H17 differentiation [20, 28, 31, 32]. While heightened glycolysis is necessary for T_H17 differentiation and function, HIF1 α appears to also directly regulate T_H17 differentiation, at least in part through direct transcriptional activation of the T_H17 master transcription factor ROR γ , thereby enhancing T_H17 differentiation [29, 30]. On the other hand, either the pharmacological inhibition of glycolysis or genetic deletion of HIF1 α can enhance T_{reg} differentiation, partially through antagonizing forkhead box protein 3 (Foxp3), the master transcription factor for T_{reg} differentiation [29]. Consistent with the idea that glucose catabolism provides essential metabolic precursors for fatty acid synthesis, T_H17 but not T_{reg} cells, depend on acetyl-CoA carboxylase (ACC1)-mediated *de novo* fatty acid synthesis. The inhibition of ACC1 prevents T_H17 cell differentiation whereas it promotes the development of T_{reg} cells. Importantly, pharmacological inhibition of ACC1 suppresses T_H17 cell-mediated autoimmune disease in mouse models [30]. In contrast to conventional Foxp3⁺ regulatory CD4⁺ T cells, the differentiation of type 1 regulatory T (Tr1) cells, which are Foxp3⁻ regulatory CD4⁺ T cells, requires HIF1 α -dependent early metabolic reprogramming [31, 32]. These studies and those of others further implicate the complex regulatory mechanisms and the essential role of the metabolic program in T cell subtype differentiation.

Similar to CD4 T cells, activated CD8 T cells also shift from fatty acid oxidation to aerobic glycolysis and glutamine oxidation, both of which are required to support CD8 T cell growth and differentiation into cytotoxic T cells [14, 37]. Following the stage of proliferation and differentiation, this shift is partially due to a decrease in mTOR signaling [38–40]. Such a metabolic switch is postulated to be required for the generation of memory CD8 T cells. Consistent with this idea, a recent study has shown that the enhancement of mitochondrial oxidative phosphorylation could improve long-term protective immunity through the promotion of CD8⁺ T effector and memory cell proliferation and survival in the context of viral and tumor clearance. Some of the biologic outcomes of T cells are likely attributable to the production of pro-proliferative mitochondrial reactive oxygen species (mROS) [41]. Taken together, T cell activation and differentiation are tightly coupled with metabolic reprogramming.

Metabolic plasticity

T cells are tasked with controlling invading organisms that replicate more rapidly than cellular division. It is therefore not surprising that the T cell-mediated immune response seems more like an “arms race” and that active T cells have the capacity to produce large amounts of cytokines, meanwhile undergoing replication every four to six hours, one of the shortest cell divisions in vertebrate cells [38]. In this regard, a key characteristic of the T cell is its metabolic plasticity. This is manifested by a capacity to maintain metabolic homeostasis in a wide range of conditions, including harsh microenvironments in which the T cell must continue to meet the high bioenergetic demand in order to mount a robust immune response.

T cell metabolic plasticity can be reflected by following three considerations: 1) T cells are required to function in a wide range of infection and inflammation sites throughout the body. As such, there are regional differences in the metabolic repertoire imposed by the tissues in which T cells reside, and the potential competition of nutrients with rapidly proliferating pathogens (in infection sites), tumor cells (in tumor) or other infiltrated immune cells may all tailor the T cell metabolic preference; 2) The differentiation of naive T cells into lineages with distinct functions has been considered to be of a great degree of flexibility in their lineage engaging signaling [29–32]. Such flexibility may also be a reflection of the dynamic changes on the metabolic phenotypes and fuel choices, which are associated with each lineage given the accumulating evidence showing the impact of metabolic modulation on T cell lineage commitments [3, 11, 40, 42, 43]; 3) Glucose and glutamine are considered as primary fuels for proliferating cells, such as cancer cells and active T cells. However, many other normal cells with various tissue origins use a wide range of nutrients as their primary fuels [44]. Moreover, recent emerging evidence has implicated that alternative metabolic substrates or metabolic reconstructions can compensate for the loss of glucose or glutamine in cultured cancer cells [45, 46]. Given the similarity of characteristic metabolic features between transformed cancer cells and activated T cells, we envision metabolic plasticity in terms of uptake of alternative metabolic substrates and induction of metabolic reconstruction as a built-in feature that has been evolved to allow T cells to adapt to constantly changing intra- and extracellular metabolic conditions.

While glucose is required to fuel T cell survival and proliferation, we have previously shown that some active T cells can survive in the absence of glucose, indicating that other nutrients/metabolites partially compensate for the loss of the primary nutrient in order to enable the survival of T cells [2]. This is further supported by the recent finding that galactose can replace glucose to support T cell survival and proliferation following activation [47]. There is a wide range of common naturally occurring monosaccharide sugars, such as D-glucose, D-galactose, D-fructose, D-mannose, D-lactose and D-ribose, that have similar chemical properties and bioenergetic value in terms of carbon and hydrogen numbers and chemical bonds. While the catabolic pathway of these sugars in vertebrate cells remains incompletely understood, metabolic studies in prokaryotic organisms or in eukaryotic microorganisms have revealed that many of these sugars share similar catabolic routes, raising the possibility that vertebrate cells may have a similar degree of metabolic plasticity on the choice of consuming monosaccharide sugars. The ribose salvage through nucleotide or nucleoside

catabolism may also provide an important carbonaceous and bioenergetic source under the condition of nutrient scarcity [48]. Beyond the plasticity of the choice of sugar as carbonaceous and bioenergetic source, some cancer cells can also utilize acetate and ketone bodies as alternative metabolic substrates [49–51]. In addition, a wide range of abundant energy-generating carbohydrates in plasma could be a source of nutrients for T cells and other proliferative cells *in vivo* [46]. T cells migrate to and function in a wide range of nutrient-deficient environments, such as infectious, inflammatory and tumor sites. It is conceivable to speculate that the ability of T cells utilizing alternative nutrients in these environments is critical in supporting and shaping the T cell-mediated immune response.

Beyond glucose, glutamine is the other primary metabolic substrate for proliferative cells such as T cells and cancer cells [2, 15, 52–54]. However, asparagine, one of the nonessential amino acids, is sufficient to replace glutamine-dependent survival of proliferating cancer cells, including transformed T cells [55]. Also, we have revealed that the supplementation of naturally occurring metabolites, polyamines and nucleotides, can partially compensate for the loss of glutamine in order to continue to support T cell growth and proliferation [2]. One of the key adaptive responses following glutamine starvation is the induction of autophagy [56]. Through recycling available organelles and macromolecules into bioenergetics resources, autophagy is an essential cellular process for maintaining energy homeostasis when nutrients are limited, and thus may represent another important layer of metabolic plasticity. Supporting this idea, emerging evidence has shown that the machinery involved in autophagy is critical for T cell development, activation and differentiation [57–61]. While autophagy is required for scavenging intracellular macromolecules, proliferating cancer cells are also able to scavenge extracellular macromolecules, such as glycogen, protein and lipids, in the face of nutrient scarcity [35, 62, 63]. This is likely a shared characteristic between proliferative cancer cells and proliferative T cells.

As the end product of glycolysis, lactate is generally considered metabolic “waste”, the concentration of which ranges from 1 to 30mM under physiological and pathological conditions in vertebrate plasma [64]. Muscle cells, neurons, and some tumor cells can utilize lactate as a prominent substrate that fuels oxidative metabolism [65–67]. Interestingly, the uptake of lactate can be induced in T cells following activation, implicating lactate as an alternative energy source by T cells (which has not been formally examined) [68]. Consistent with this idea, lactate supplementation can stimulate cytokine production in T cells following activation and differentiation [69–72]. However, the immunoregulatory effect of lactate on T cells seems to be dependent on the cellular context and the dose of lactate applied in these studies since lactate can either enhance or impair human CD4⁺ T cell proliferation at low or high concentrations, respectively [73].

Additional evidence implicating that T cell subset differentiation can be driven by the microenvironment is demonstrated in specific tissues and disease states, in that even after differentiation cellular phenotypic changes can occur. T cell polarization can be dramatically affected by the surrounding metabolic environment in the central nervous system (CNS). Astrocytes produce glutamate and in CNS disease it has been noted that extracellular glutamate levels are increased, with subsequent studies showing that this results in a shift toward the T_H1 phenotype and polarization of T_{reg} cells [74]. Also, undifferentiated CD4 T

cells cultured in the absence of glucose have no effect on the generation of T_{reg} cells. Among alloreactive T cells, a reciprocal increase of the intracellular fatty acid oxidation intermediate acylcarnitines, and decrease of extracellular fatty acids has been recently revealed [75], suggesting that fatty acids may serve as a mitochondrial substrate in some T cells. Supporting this idea, fatty acids have been suggested as a preferred fuel for T_{reg} and T memory cells [5, 33, 45]. The addition of fatty acids at initiation of activation of T_{reg} cells increases the expression of Foxp3 [5]. Also, when fully differentiated T_{reg} cells were exposed to a lipid rich environment the cytokine production was noted to increase [5]. Recent studies further reveal that commensal microbe-derived short-chain fatty acids, butyrate and propionate, promote the differentiation of regulatory T cells [76, 77]. While butyrate may impact T cell differentiation through inhibiting histone deacetylase (HDAC) activity, butyrate is also revealed as the primary energy source of normal colonocytes and is metabolized to acetyl-CoA, which was shown to be important for energetics and also for HAT activity [78]. In addition, the differentiation and homeostatic maintenance of memory CD8⁺ T cells relies on the engagement of FAO [42, 79]. However, recent studies suggest that extracellular lipids are unlikely to be the major resource for fueling memory CD8⁺ T cells. Instead, heightened glycerol uptake and subsequent synthesis of triglyceride are required to meet energy demands of memory CD8⁺ T cells [80, 81]. While glycolytic intermediates could be converted into glycerol in cells with a high rate of glycolytic flux, the direct uptake of extracellular free glycerol provides an alternative bioenergetic resource and may play an important role in maintaining cellular bioenergetics in memory CD8⁺ T cells. These studies implicate that the metabolic plasticity may interconnect with signaling-driven T cell lineage plasticity.

The recent breakthroughs in modulating T cell-mediated anti-tumor immune response to cure or significantly improve survivorship in some malignancies provides the exciting possibility of extending this approach to many types of tumors. However, tumors employ a plethora of immunosuppressive strategies, including fostering a deranged/hostile metabolic microenvironment, in order to counteract the anti-tumor immune response [82–84]. Heightened consumption of glucose and amino acids, such as glutamine, tryptophan, cysteine, glycine and arginine are common features in most cancer cells [85–91]. As such, the tumor microenvironment represents a dramatic example of metabolic derangement, where the highly metabolic demanding tumor cells often contribute to the depletion of glucose and essential amino acids and may compromise the function of anti-tumoral cytotoxic CD8⁺ T cells and CD4⁺ effector cells by competing for nutrients (a form of metabolic antagonism). On the other hand, the immune-checkpoint mechanism that is largely elicited through cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD1) plays a key role in immune resistance. As such, the therapeutic approaches that target immune-checkpoint and therefore unleash anti-tumor immunity have achieved important clinical advances in threatening several types of tumors [92–96]. Interestingly, recent studies suggest that antibody-mediated blockade or genetic deletion of CTLA-4 or PD1 could enhance glucose consumption in T effector cells [97–99]. It is therefore tempting to speculate that the strengthened anti-tumor immune response, following dampening of the immune-checkpoint, is partially due to heightened metabolic fitness of immune cells. The adoptive transfer of naturally occurring or gene-engineered T cells has

emerged as another powerful form of immunotherapy. However, in order to exert a robust anti-tumor response, adoptively transferred T cells must efficiently overcome the metabolic restrictions of the tumor microenvironment in order to survive, proliferate and remain functional [100–102]. Thus, the complete understanding of metabolic plasticity of T cells may lead to novel manipulative metabolic approaches that can skew T cells to generate robust and sustainable anti-tumor immune responses.

Conclusion and Perspective

The revived interests in T cell metabolism has revealed many fundamental biological insights and will likely generated new therapeutic strategies for immunological diseases in the near future. We summarize here that there is emerging evidence of characteristic metabolic events associated with T cell function and further vision that modulation of the T cell metabolic pathway may offer novel therapeutic regimes to improve immunological unresponsiveness or to suppress excessive immune responses in various pathological conditions. To win the battle against rapidly replicating invading pathogens, vertebrates have evolved a complex lymphatic system to rapidly deploy lymphocytes to infection and inflammation sites throughout the body. As such, T cells must respond and adapt to the wide vagaries of the metabolic landscape (nutrient pools) imposed by these infectious and inflammatory sites in different tissues. Inevitably, such responsiveness and adaptation reflects metabolic plasticity, allowing T cells to elicit robust immune functions in a wide range of metabolic microenvironments. Finally, such knowledge may also help to reveal the impact of conditions of metabolic disease and nutritional imbalances on immune responses.

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Highlights

1. T cells undergo a metabolic rewiring during activation and differentiation.
2. T cells are capable of responding to and adapting to nutrient fluctuations.
3. T cells change metabolic substrates and routes in response to nutrient fluctuations.
4. Metabolic plasticity allows T cells to maintain metabolic homeostasis.

Figure 1.
Metabolic reprogramming in T lymphocytes