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T cell Metabolism – Regulating Energy

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Abstract

Antigenic stimulation of T cells initiates a change from the resting state into an activated one mediated by triggering the T cell receptor (TCR). This change is characterized by rapid proliferation, differentiation and acquisition of effector functions. To maintain the energetic needs accompanied by this processes, T cells are able to adapt their uptake and utilization of extracellular nutrients. Proliferation and differentiation into distinct subsets of T lymphocytes like effector-, regulatory-, and memory T cells is mediated by antigens, various cytokines and growth factors through their respective signaling pathways they trigger. Since these subsets acquire different functions in the immune system, their metabolic profiles also differ. Throughout the last decade the role metabolism was intensively investigated and evolved into one major part in understanding activation and differentiation processes in T cells. Key molecules like AKT and AMPK were described to be major regulators of metabolism. Therefore, we discuss in this review which signaling molecules are known regulate metabolic pathways in T cells and we give an overview over the mechanisms how they accomplish this task.

Keywords: T cell; Regulatory molecules; Metabolism

Introduction

T cells play a central role in the immune system and are important for cell mediated immunity. A functional immune response requires rapid cell growth, proliferation, and the production of effector proteins. In the presence of specific antigens T lymphocytes must rapidly shift from a resting state to an activated one to accomplish these tasks. The activation of T cells is accompanied by a huge demand for ATP; the universal energy carrier in cell metabolism. The main processes to generate ATP are glycolysis and the citric acid cycle followed by oxidative phosphorylation. In resting T cells oxidative phosphorylation was described to be the central energy producing process [1,2]. Furthermore it was described that upon activation the energy produced by oxidative phosphorylation in resting cells is not sufficient. Therefore lymphocytes undergo a metabolic shift to an increased glycolytic rate, which leads in turn to lactate production [3-5]. This reprogramming of cellular metabolism is described in the literature as anaerobic glycolysis for example during intense muscular activity [6] where myocytes switch their metabolism under "working" conditions, in the absence of oxygen, towards elevated levels of glucose transport and high rates of glycolysis. However Otto Warburg first observed these features for cancer cells in the presence of oxygen [7] therefore it was called "aerobic glycolysis". Aerobic glycolysis was long thought to be a feature unique to cancer cells. However, we now know that the Warburg effect is also observed during the rapid proliferation of primary T cells, and it is viewed as a general feature of anabolic metabolism [5,8]. Anabolic metabolism is a characteristic feature of proliferating cells, which have to synthesize all cellular material in order to form two daughter cells. Therefore they require energy carriers like ATP and macromolecular precursors to generate biomass in form of proteins, ribonucleotides and lipids. By upregulating their glycolytic rate, cells become capable to maintain these anabolic mechanisms.

In the last years the focus shifted from metabolism itself to the question of how T cells regulate this metabolic shift. During the immune response T cells become activated by triggering of the T cell receptor, which initiates specific signaling events. This includes the activation of the phosphoinositide-3-kinase(PI3K)/Proteinkinase B (AKT) pathway, mammalian target of rapamycin (mTOR), and adenosine-monophosphate- activated protein kinase (AMPK), which were shown to play a central role in regulating T cell metabolism [2,4,5,9,10]. In this review we will focus on AKT and AMPK, how these signaling molecules can regulate metabolic pathways in T cells and provide an overview of potential mechanisms used to accomplish this task.

Changes in T cell Metabolism upon Activation

Resting T cells require relatively low amounts of energy for housekeeping functions, i.e. homeostasis. Most of this energy is produced by oxidative phosphorylation (OXPHOS) through the degradation of glucose, fatty acids, and glutamine [1,2]. Upon activation, cellular programs direct T cells towards proliferation, differentiation, and cytokine production. The subsequent need for energy and metabolic precursors was shown to be accomplished by a strong upregulation of glycolysis [4,11], which is characterized by an increased uptake of glucose, increased expression of glycolytic enzymes and the generation of lactate from pyruvate. Although the generation of ATP by glycolysis is inefficient when compared to OXPHOS (2ATP<36ATP), upregulating glycolysis has the advantage of being a fast process and was shown to protect cells against apoptosis [11-13]. Since upregulating glycolysis without a corresponding increase in OXPHOS would lead to an accumulation of the end product pyruvate, it was shown that the excess pyruvate generated is converted to lactate by lactate dehydrogenase [4,14]. This step is essential to regenerate the reducing agent NADH, which is needed to maintain the high glycolytic turnover. Since high concentrations of lactate are toxic to the cells, the lactate produced is also secreted.

These observations lead to the conclusion that glucose is the major

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energy source of activated lymphocytes. This was also confirmed by showing that removing glucose in activated T cells leads to an inhibition of T cell proliferation and cytokine production [11]. In addition, also other metabolic pathways have been shown to play a role in T cell metabolism, e.g. increased glutamine consumption was shown to be essential for T cell function [8,15,16]. Glutamine is degraded via the TCA cycle, providing a nitrogen source for non-essential amino acids and nucleotides, and refilling the intermediates of the TCA cycle which are also used for biosynthetic processes that are essential for maintaining T cell proliferation [8]. At the end of the TCA-cycle malate dehydrogenase converts the generated malate to pyruvate. This pyruvate together with an upregulated glycolysis can foster the generation of lactate. Beside the generation of ATP, T cells also require NADPH to support lipid and nucleotide biosynthesis. NADPH is generated in two different processes, the pentose-phosphate-pathway dependent on glucose-6-phosphate and the last step of glutamine degradation – the conversion from malate to pyruvate. This suggests that glucose and glutamine are the major nutrients needed for proliferation in T cells.

AKT and AMPK in T cell Metabolism

The most prominent pathway responsible for upregulating glycolysis is the PI3K/AKT pathway. In T cells, coligation of the TCR and CD28 lead to direct phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP_2) by phosphoinositide 3-kinase (PI3K) which leads to increased levels of phosphatidylinositol-3,4,5-trisphosphate (PIP_3). AKT translocates to the plasma membrane by binding PIP_3 via its PH-domain, where it can be phosphorylated by PDK1 on Thr308. For full activation, AKT requires additional phosphorylation on Ser473 by mTOR complex 2. It was shown for Tcells that sustained activation of AKT upregulates the surface expression of glucose transporter 1 (GLUT1) and increases the activity of the rate-limiting glycolytic enzyme hexokinase [4,17]. A previous study by McIntyre [18] reported that AKT had no effect on glucose uptake in $CD8^+$ T cells. The authors of this study suggested that the upstream kinase PDK1 is responsible for increased glucose uptake and is therefore dispensable for $CD8^+$ T cell metabolism. A study done in our lab came to the same conclusion when analyzing glucose uptake. But there was strong evidence that AKT is needed for upregulation of lactate dehydrogenase (unpublished results). The three major regulating enzymes of glycolysis are hexokinase, phosphofructokinase and pyruvate kinase. Although a link between AKT and pyruvate kinase was not investigated so far, the observations that AKT regulates the activity of hexokinase and phosphofructokinase [17] leads to the hypothesis that AKT is responsible for upregulating enzymes of glycolysis and lactate production. Additionally PDK1 or other members of the AGC kinase family can be responsible for increased glucose uptake in T cells. Since this contradicts the results of previous studies [4,11], the experimental conditions need to be critically discussed (Figure 1). The observations on the activating role of AKT were mostly performed in primary human T cells stimulated with CD3 and CD28, which fully activate AKT. This led to upregulation of GLUT1 expression and glucose uptake which could be inhibited by addition of cytotoxic T-lymphocyte antigen 4 (CTLA4) [4]. The recent studies observing a dispensable role of AKT were done in murine $CD8^+$ T cells under physiological conditions using peptide stimulations without costimulation. Since it was shown before that $CD8^+$ T cells do not require costimulation via CD28 [19] this might also lead to different outcomes in metabolic regulation. It was shown before under physiological conditions that the activation of AKT is sustained, but weak [20]. It might be that under these conditions a weak activation of AKT leads to compensatory mechanisms which also induce glucose uptake and GLUT1 upregulation. Possible targets of this mechanism could be the activation of PDK1 or the activation of the MAP-kinase ERK, which was also shown to be responsible for upregulated glucose uptake [21].

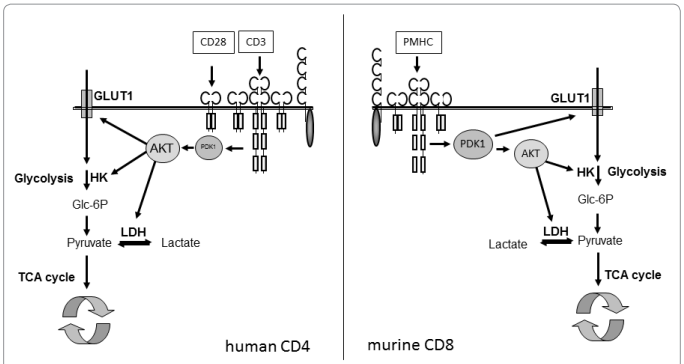

Figure 1: Different regulatory functions on AKT and PDK1 on human CD4 and murine CD8 T cells.
GLUT1: Glucose-Transporter 1; HK: Hexokinase; LDH: Lactate dehydrogenase.

Another important regulator of cellular metabolism is AMPK, which promotes ATP conservation and production through the activation of glycolysis, fatty acid oxidation, and the inhibition of ATP-consuming pathways, such as protein synthesis, fatty acid synthesis, gluconeogenesis, and glycogen synthesis [22,23]. AMPK can be activated by an increase in the AMP:ATP ratio followed by phosphorylation through LKB1 (a serine/threonine kinase). In addition it has been shown that Ca^{2+}-calmodulin-dependent kinase kinase 2 (CAMKK2) can activate AMPK independent of AMP levels [24]. Recently, it was found that LKB1 is essential for the survival of thymocytes and development of T-cell progenitors and is required for $CD4^+$ and $CD8^+$ T-cell development [25,26]. LKB1-deficient peripheral T cells were shown to have enhanced glucose uptake and a higher glycolytic rate [25,26]. This suggests that LKB1/AMPK antagonize the PI3K/AKT/mTOR pathway, which promotes anabolism. This could be confirmed by the observations that AMPK inhibits mTOR activity [25] and that activation of AMPK was shown to be transient upon T cell stimulation [24]. Additionally, AMPK was shown to be required for memory T cell differentiation. Addition of the drug metformin caused an sustained activation of AMPK and subsequently led to increased numbers of memory T cells. Recent studies showing that LKB1/AMPK influences assymetric cell division in *D. melanogaster* [27-29], suggest that there could be a role for AMPK in the assymetric divisionT cells [30]. Since sustained activation of AKT is needed for effector T cell differentiation and AMPK activation appears to be only transient under these conditions, one could hypothesize that the contact of a T cell to an APC could also lead to a polarized distribution of metabolites. In this scenario the half of the T cell containing the immunological synapse would differentiate into an effector T cell, whereas the distal part would lead to memory T cell formation (Figure 2). While this hypothesis is attractive, it requires further investigation.

Recently several studies have further analyzed the connection between the major metabolic regulators and metabolism. It was investigated whether transcription factors like HIF1a (hypoxia inducible factor1a) and MYC play an important role in expression of metabolic enzymes. Hif1a is a transcription factor that regulates the expression of genes that encode for glycolytic enzymes [31] as well as downregulates mitochondrial oxygen consumption by blocking the entrance of pyruvate into the TCA cycle [32]. Hif1a is constitutely

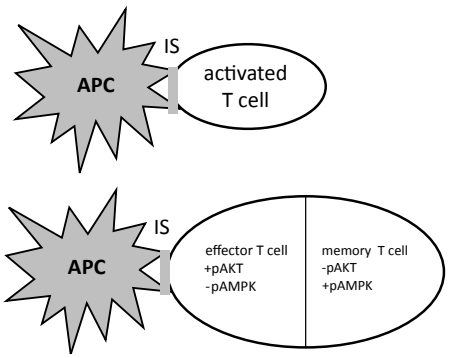

Figure 2: Different metabolic programs in asymmetric cell division-AKT and AMPK influence the generation of effector and memory T cells.

active, but under normoxic conditions, it is rapidly degraded. Under low oxygen conditions the degradation of Hif1a is inhibited and it translocates to the nucleus where it upregulates glycolytic genes and drives the cell towards aerobic glycolysis. A recent study showed that the activation of $CD4^+$ and $CD8^+$ T cells leads to a strong, but transient induction of HIF1a. However, this activation was not responsible for metabolic changes in these cells and was not critical for proliferation [33]. In addition, another study observed that HIF1a is strongly induced only in the TH17 subset [34]. Another factor investigated was the proto-oncogenic transcription factor Myc, which was shown to be induced upon T cell stimulation [15]. The deletion of Myc lead to an impaired upregulation of glycolysis and glutaminolysis, and a decreased activation of targets downstream of mTOR. These observations led to the conclusion that Myc is probably the major transcription factor regulating T cell metabolism upon activation. Taking together all studies on T cell metabolism, it becomes clear that different T cell subsets have different metabolic profiles. $CD4^+$ and $CD8^+$ effector cells show strong activation of glycolysis and lactate production, mediated via PI3K/AKT pathway, which correlates with their ability to proliferate and produce cytokines that promote a productive immune response. In contrast, both regulatory T cells (Tregs) and memory T cells fail to upregulate glucose metabolism [35]. Their demand for glucose is much lower and is replaced by using lipids as an energy source through ß-oxidation. This is also compatible with their function, as Tregs and memory T cells are long-lived cells witha slow rate of replication.

Summary

Primary T cells are able to upregulate metabolism from a quiescent to an activated one in order to maintain their energetic needs for proliferation, differentiation, and cytokine production. The PI3K/AKT pathway plays a central role in regulating T cell metabolism. Understanding T cell metabolism provides insight into how T cells can deal with their energetic needs and how this may affect their function. The ability of T cells to switch between states of low and high energy consumption, which then in turn drives them towards their specific function, shows the interplay between signalling events and the metabolic program. Improving our understanding as to how these processes are regulated will not only provide insight in to how immune cells function, but it may also reveal targets for suppressing T cell-mediated autoimmune diseases or provide tools to improving the immune response.

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Conflict of Interest

The authors declare no competing financial interest.

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