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This information is current as of September 28, 2021.

J Immunol 2004; 172:4661-4665; ;
doi: 10.4049/jimmunol.172.8.4661
<http://www.jimmunol.org/content/172/8/4661>

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BRIEF REVIEWS

Regulation of T Lymphocyte Metabolism

Kenneth A. Frauwirth* and Craig B. Thompson^{1†}

Upon stimulation, lymphocytes develop from small resting cells into highly proliferative and secretory cells. Although a great deal of study has focused on the genetic program induced by Ag receptor signals, lymphocytes must also regulate their metabolic function to meet the energetic demands of activation. In this review, we discuss the changes in cellular metabolism that accompany lymphocyte activation, with a particular emphasis on glucose metabolism, a major source of both energy and biosynthetic building blocks. We will also cover the signaling pathways that positively and negatively regulate these changes to maintain metabolic homeostasis in cells that are rapidly growing, dividing, and differentiating. The Journal of Immunology, 2004, 172: 4661–4665.

Lymphocytes must be able to rapidly respond to the presence of pathogens, shifting from a quiescent phenotype to a highly active state within hours of stimulation. Most investigation has centered on the signal transduction pathways that lead to the transcriptional activation of cell cycle control genes and immune effector molecules. More recently it has been recognized that macromolecular synthesis must also be up-regulated to allow the cell to enact the transcriptional programs of growth, proliferation, and effector function. In contrast, relatively little attention has been focused on how lymphocyte metabolism is regulated to support the bioenergetically demanding processes of growth. Activated lymphocytes must dramatically alter their metabolism to support these increased synthetic activities. Classical biochemistry teaches that cellular metabolism is homeostatically regulated, such that an increased demand for energy or biosynthetic intermediates leads to derepression of catabolic pathways in response to the increased conversion of ATP to ADP. Although such compensatory changes can prevent an acute bioenergetic collapse in response to the initial increase in energy consumption associated with signal transduction and transcription, there is growing evidence that extracellular signals are required to up-regulate lymphocyte nutrient uptake and metabolism to support cell growth, proliferation, and cytokine secretion. This opens the possibility that the signaling pathways involved in lymphocyte metabolic control may be novel therapeutic targets.

Metabolism in resting lymphocytes

When T lymphocytes exit the thymus, they enter peripheral circulation as small quiescent cells. These resting T cells consume glucose and other essential nutrients at a low rate (1–3), supplying energy to maintain normal housekeeping functions (4). Glucose utilization is divided approximately evenly between oligosaccharide synthesis (glycosylation reactions), lactate production (glycolysis only), and oxidation to CO₂ (glycolysis plus Krebs cycle; pentose phosphate pathway) (1). To maintain even this basal metabolic rate, T cells require extracellular signals, including cytokines and low-level stimulation through the TCR. In the absence of such signals, T cells reduce their capacity to import glucose to levels below those necessary to maintain cellular homeostasis (5, 6). Thus, the metabolism of resting lymphocytes is limited by the availability of trophic signals rather than by the availability of nutrients.

Activation by mitogens and aerobic glycolysis

Early studies of T cell activation used mitogenic plant lectins, such as Con A, PHA, and pokeweed mitogen. Treatment of bulk T cells with these mitogens leads to activation similar to antigenic stimulation, including cell growth (blastogenesis) and proliferation, but affecting the majority of T cells in a population, rather than the small number of cells responsive to a specific Ag. Not surprisingly, the energy-demanding processes of mitogenic activation are accompanied by an increase in glucose utilization, detectable within 1 h of stimulation (1, 7–9).

Stimulation also induces a rapid but moderate elevation in oxygen consumption (1, 7, 10); however, the increase in glycolysis is dramatically greater than the increase in oxygen consumption, resulting in a significant increase in the production of lactate. This development of a highly glycolytic metabolism has been called “aerobic glycolysis,” distinguishing it from the shift to glycolysis caused by oxygen limitation (as in muscle). Aerobic glycolysis was originally described as a constitutive feature of many malignant cells (11) and may represent a consequence of specific oncogenic mutations acquired during transformation.

There are two major interpretations of the switch to aerobic glycolysis during lymphocyte activation. Lymphocytes may be unable to increase oxidative phosphorylation enough to supply their energy needs and must therefore hyperinduce glycolysis.

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Received for publication December 19, 2003. Accepted for publication February 23, 2004.

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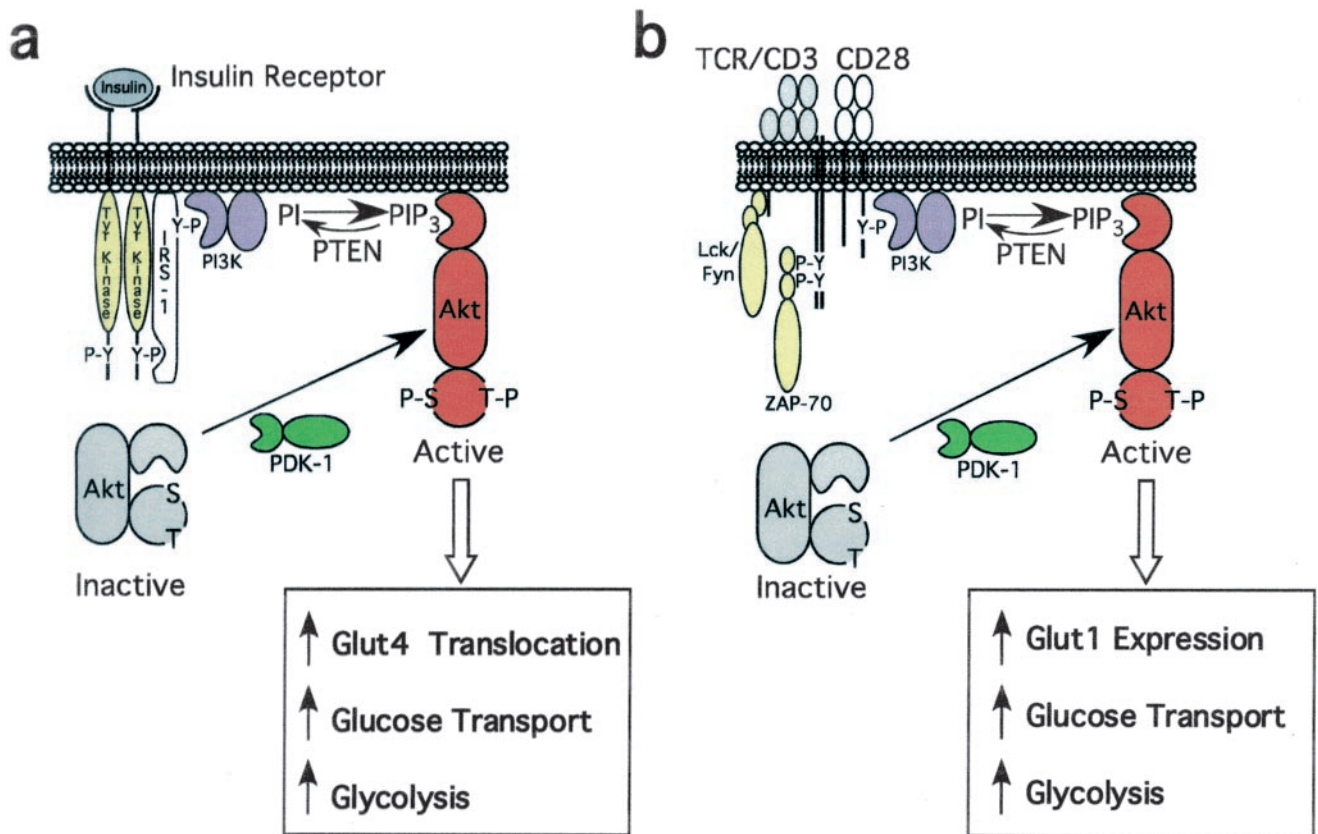


FIGURE 1. Insulin and costimulation regulate analogous metabolic control pathways. *a*, Binding of insulin to the insulin receptor triggers intrinsic tyrosine kinase activity, leading to recruitment and phosphorylation of the adaptor protein IRS-1, followed by recruitment and activation of PI3K. PI3K generates PIP₃, which recruits Akt to the plasma membrane, where it can be activated by the PI3K-responsive kinase PDK-1. Active Akt is able to promote redistribution of Glut4 from intracellular stores to the cell surface, increased Glut1 expression, and enhanced glucose transport and glycolysis in insulin-responsive cells. *b*, Coligation of the TCR complex and CD28 on T cells leads to phosphorylation of CD28 and recruitment of PI3K. As in *a*, active PI3K leads to activation of Akt, with the metabolic effects of increased Glut1 synthesis and surface expression, and enhanced glucose transport and glycolysis.

Alternatively, the shift to glycolysis could result from a primary stimulation of glucose uptake and catabolism that exceeds the cell's demand for glucose-derived macromolecular precursors or NADH, which is used to produce ATP through oxidative phosphorylation. Under conditions in which the cell's glycolytic rate exceeds its bioenergetic needs, the excess pyruvate plus NADH produced will drive the formation of lactate, allowing the cell to regenerate its pool of NAD⁺. However, it is clear that glucose metabolism does not increase simply in response to the increased ATP to ADP conversion that occurs during lymphocyte activation. Inhibiting glycolysis with 2-deoxyglucose in the presence of alternative Krebs cycle substrates (aspartate plus acetate) blocks PHA-induced proliferation, despite maintaining energy-generating capacity (7), indicating that glycolysis provides something that cannot easily be derived from Krebs cycle reactions.

In addition to the enhancement of glycolysis, T cell activation also leads to changes in other pathways of glucose utilization. A major alternative to glycolysis for glucose metabolism is the pentose phosphate pathway, also known as the hexose monophosphate pathway. This pathway allows the generation of pentose sugars required for nucleic acid synthesis and is also a source of NADPH for reductive biosynthetic reactions. Compared with resting cells, actively growing and proliferating cells have increased demand for both pentose sugars and NADPH. T cell stimulation by mitogens activates the pentose phosphate pathway (8). The activity of this pathway peaks by 48 h of stim-

ulation, coinciding with the maximal protein and RNA synthesis of T cell blastogenesis.

Costimulation and aerobic glycolysis

Activation of T cells requires two distinct signals: The TCR (signal 1), which provides Ag specificity, and costimulatory receptors (signal 2), which inform the T cell of the presence of an inflammatory environment. Although lectin stimulation of T cells appears similar to activation through the Ag receptor, it is likely due to cross-linking of many different surface molecules, making it difficult to isolate the specific receptors and pathways involved in metabolism regulation. However, the examination of metabolic control in other cell types may be informative in understanding the analogous processes in T cells. The insulin signaling pathway is a major control system for glucose metabolism in several cell types, including muscle and fat. The binding of insulin to its receptor leads to the activation of phosphatidylinositol 3-kinase (PI3K)² and its downstream effector Akt, which in turn induces glucose transport and utilization (12–14) (Fig. 1*a*). In T cells, ligation of the costimulatory receptor CD28 similarly activates the PI3K/Akt pathway (15), marking CD28 as a candidate for regulating T cell metabolism (Fig. 1*b*). Stimulation of resting T cells with anti-CD3 plus anti-CD28, but not anti-CD3 alone, leads to changes in glucose utilization

² Abbreviations used in this paper: PI3K, phosphatidylinositol 3-kinase; PFK, phosphofructokinase; mTOR, mammalian target of rapamycin; AMPK, AMP-dependent protein kinase.

similar to those seen with mitogenic lectins or treatment of insulin-responsive tissues with insulin. T cells increase glucose transporter expression, glucose uptake, and glycolysis in response to CD3/CD28 stimulation, and these effects are dependent on PI3K activity (3). As with lectin stimulation, CD3/CD28 stimulation also leads to only a moderate increase in oxygen consumption and thus the bulk of carbon the cell takes up as glucose is secreted as lactate. Thus, activation of T cells in the presence of costimulatory signals is accompanied by induction of aerobic glycolysis, resulting from an Akt-dependent stimulation of glucose uptake.

The precise function of costimulation in T cell activation is still a matter of significant debate. Because ligation of CD28 alone has little effect on resting T cells, it is unclear whether costimulation simply magnifies TCR proximal signals or whether it contributes a novel, synergistic function. The role of costimulatory signals in regulating glucose uptake and glycolysis suggests the latter, as might be summarized in a two-pronged model (Fig. 2). In one branch, TCR signals induce a transcriptional program, which is enhanced but not dramatically altered by costimulation (16). This program places a significant energy demand on the cell due to increases in macromolecule synthesis and other energy-consuming processes. A compensatory response of the cell is its use of oxidative phosphorylation to increase the ATP production from the limited pool of glucose and glycolytic precursors available to it. In the second branch, costimulatory signals up-regulate the surface expression of glucose transporters and increase the production of ATP and the pool of macromolecular precursors. Because much of glucose metabolism is controlled posttranscriptionally, glucose uptake can be dramatically and rapidly up-regulated through costimulation to levels that exceed bioenergetic demand, which prevents a bottleneck during T cell activation (3). Such a model would predict

that activation of both branches simultaneously would have a synergistic ability to increase transcription and translation.

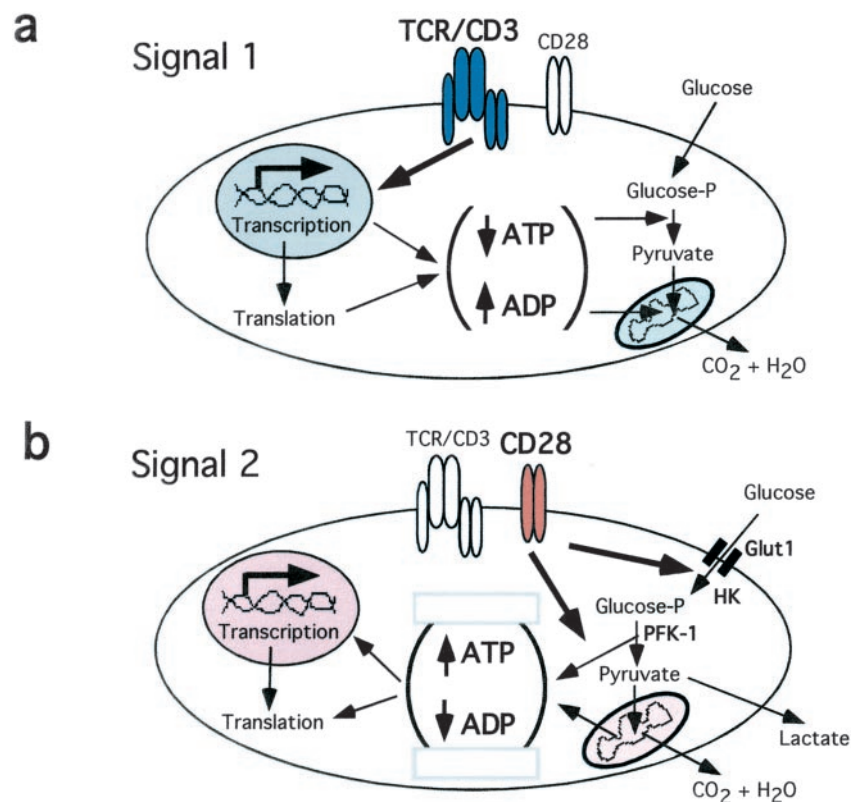
Activation of T cells is opposed by inhibitory receptors, such as CTLA-4. These receptors can block many early activation events and may work, at least in part, by antagonizing costimulatory signals. Consistent with this idea, CTLA-4 can inhibit CD28-induced increases in glucose metabolism (3). This raises the interesting possibility that disruption of metabolic function is an important mechanism of action of inhibitory receptors, allowing them to interfere with a wide range of cellular functions by choking off the supply of glucose-derived energy and biosynthetic intermediates.

Regulation of glucose metabolism by Akt

As described above, induction of glucose metabolism during T cell stimulation is dependent on the activation of PI3K. Akt has been shown to control changes in glucose transport and metabolism downstream of the insulin receptor (12–14), and constitutively active Akt stimulates glucose transport and glycolysis in multiple cell types, including primary lymphocytes (3, 17–19). Thus, it is likely that Akt is the PI3K-dependent factor controlling glucose metabolism downstream of costimulatory signals. However, the specific targets of Akt critical for metabolic control have not been well defined.

Enhancement of glucose transport by insulin is largely mediated by translocation of the glucose transporters from intracellular stores to the plasma membrane. In lymphocytes, the major glucose transporter is Glut1 (5), and Akt activity increases both expression and cell surface localization of Glut1 (17, 20, 21). During T cell activation, increased glucose transport is detectable well before increased Glut1 expression (our unpublished

FIGURE 2. The T cell “two-signal” hypothesis can be interpreted in terms of metabolic demand and supply. *a*, Signals from the TCR-CD3 complex induce a gene expression program, placing a large metabolic demand on the T cell, introducing a potential energy bottleneck during activation. *b*, Signals from CD28 directly enhance glycolysis, increasing cellular stores of energy and biosynthetic substrates and allowing the TCR/CD3-mediated gene expression program to proceed. HK, hexokinase.



observations), indicating that changes in Glut1 intracellular localization are likely responsible for at least early changes in glucose uptake. However, the mechanism by which Akt regulates Glut1 localization is unknown.

Increased glucose transport capacity alone cannot explain increased glycolysis, since glucose can adopt several fates in a cell or can simply diffuse back out via the glucose transporters. A second critical control step in the glucose uptake is the phosphorylation of glucose by hexokinase, trapping glucose in the cell and allowing it to enter the glycolytic pathway (although not excluding other fates). Akt increases total cellular hexokinase activity (21) as well as mitochondrially associated hexokinase activity, which may be important in coupling glycolysis with mitochondrial function (22). However, there is currently no evidence that hexokinase is a direct target for Akt. Thus, as with Glut1 translocation, Akt regulation of hexokinase is by an as yet unknown mechanism. Furthermore, unlike constitutive Akt activity, overexpression of Glut1 plus hexokinase is unable to significantly increase either the glycolytic rate or total cellular glucose consumption, despite increasing glucose transport capacity (21).

The key rate-limiting step in glycolysis is the phosphorylation of fructose 6-phosphate by 1-phosphofructokinase (PFK), generating fructose 1,6-bisphosphate. This is also the step that fully commits glucose to glycolysis. PFK-1 activity is controlled by allosteric regulators, and one such regulator is fructose 2,6-bisphosphate, the product of PFK-2 activity and a potent activator of PFK-1 (23, 24). Significantly, phosphorylation by Akt can activate PFK-2 *in vitro* (25). Enhanced PFK-2 activity would increase fructose-2,6-bisphosphate levels and, as a consequence, PFK-1 activity. Thus, Akt appears to act as a coordinator of glycolytic function, coupling glucose transport with increased activity of key glycolytic enzymes.

Consistent with a central role in regulating lymphocyte glucose metabolism, Akt is also subject to control by inhibitors of T cell activation. Cross-linking CTLA-4 completely blocks CD28-induced Akt activity (3). Intriguingly, CTLA-4 associates with the serine/threonine phosphatase PP2A (26), of which Akt is a direct target (27). Confirming the importance of this association, inhibition of PP2A by okadaic acid abrogates the ability of CTLA-4 to block Akt activation.

The lack of specific inhibitors for Akt has made it difficult to go beyond correlating Akt activity with lymphocyte glucose metabolic function, since factors that regulate Akt also regulate multiple other pathways. However, mice deficient in either one or two of the three mammalian Akt isoforms have been generated over the past several years (28–31). Analysis of function and metabolic control of lymphocytes from these mice will help clarify the specific role of Akt in regulating glucose metabolism, in both resting and activated cells.

Regulation of other metabolic pathways

Glucose metabolism, while certainly important, is unlikely to be the only component of cellular metabolism actively regulated during T cell activation. In transforming from a quiescent state to an actively growing and proliferating cell, a T lymphocyte must coordinate cellular energetics with increased macromolecule biosynthesis. A central regulator of this process is the mammalian target of rapamycin (mTOR). Inhibition of mTOR by the macrolide antibiotic rapamycin leads to cell cycle arrest and mimics many features of amino acid starvation (32).

Rapamycin is also a potent T cell immunosuppressant, indicating the importance of mTOR function during T cell activation (33). mTOR regulates protein synthesis via multiple phosphorylation targets, including p70S6 kinase, a regulator of ribosome function, and 4E-BP1, an inhibitor of translation (32). mTOR also directs the cell surface expression of a wide variety of nutrient transporters, including amino acid transporters, low-density lipoprotein receptor, and transferrin receptor, in response to Akt signaling (34). In T cells, surface expression of the amino acid transporter component 4F2 H chain (4F2hc) is induced by CD28 costimulation in a rapamycin-sensitive fashion (35). Thus, control of glucose transport is coordinated with import of other nutrients required for cell growth via Akt and mTOR signaling. Recently, Akt and mTOR signaling have been linked through Akt's ability to phosphorylate the tumor suppressor, tuberin (TSC-2). TSC-2 in complex with TSC-1 functions as a tumor suppressor to inhibit mTOR. Akt phosphorylation of tuberin triggers its ubiquitination and proteasomal degradation (36). This leads to derepression of mTOR activity.

In addition to roles in directly activating metabolic machinery, Akt may also interact with other regulators of metabolism. AMP-dependent protein kinase (AMPK) is an important sensor of cellular energy stores, becoming activated when the AMP:ATP ratio increases. This leads to increases in alternative energy-generating processes, such as mitochondrial fatty acid oxidation, as well as suppression of energy-consuming processes, notably protein, cholesterol, and fatty acid synthesis (37). However, T cell growth requires net membrane synthesis so activation of AMPK rapidly suppresses cell growth. Significantly, Akt activation leads to inhibition of AMPK, apparently by blocking phosphorylation by an AMPK kinase (38). By cross-regulating another key metabolic control pathway, Akt may allow an activated T cell to increase energy output without catabolizing lipids required to synthesize new membrane for the growing cell.

The metabolic horizon

Metabolic control requires integration of input from multiple pathways, and lymphocyte metabolism is likely to involve cell type-specific components. However, most studies of the control mechanisms have used the metabolically specialized tissues of liver, muscle, and adipocytes. A greater understanding of how these pathways function in lymphocytes becomes increasingly important with the increase in the therapeutic use of drugs that alter metabolism. Furthermore, since activated lymphocytes have high metabolic demands, manipulation of the lymphocyte-specific metabolic control pathways may prove to be useful in treating diseases characterized by immune hyperactivation, including leukemias, autoimmune disorders, and graft rejection.

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