

The immune diet: meeting the metabolic demands of lymphocyte activation

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Abstract

During the adaptive immune response, lymphocytes undergo dramatic changes in metabolism that accompany the proliferative burst and differentiation into functional subsets. This brief overview focuses on recent advances in understanding the mechanisms of this metabolic reprogramming in T lymphocytes.

Introduction

The adaptive immune response of vertebrates occurs through clonal selection, an elegant process that involves large numbers of lymphocytes. Each lymphocyte bears a randomly generated receptor that, if bound by its ligand in an appropriate context (indicative of potential infection), stimulates the cell to proliferate, thereby generating many more cells with this receptor. Because the specific cells are pre-selected to remove those that might recognize "self" components, the ligands that might engage the receptors are "foreign" and, thus, may identify an invading organism and orchestrate a response. The responding cells proliferate and functionally differentiate, and ultimately clear the invader. The numbers of responding cells then decline, ultimately leaving memory cells capable of a recall response should the foreign ligands reappear.

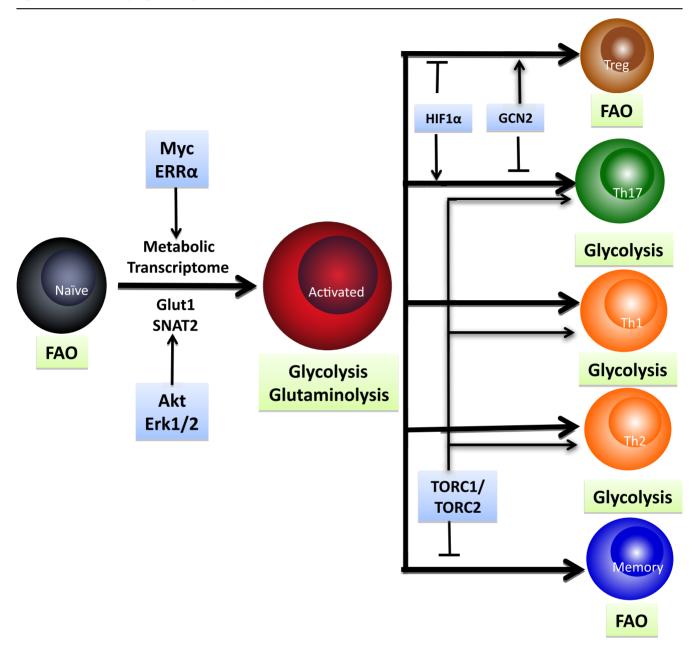
The evolution of the adaptive immune response to many pathogens is sometimes viewed as a sort of "arms race," since the invading organism may have the potential to replicate much more rapidly than the lymphocytes that would control it. It is perhaps not surprising, then, that activated lymphocytes (B and T cells) have one of the shortest cell cycles seen in mature vertebrate animals, replicating every four to six hours [1]. However, this proliferative burst is preceded by a lag phase of about 24 hours, during which the cell grows (increases mass) prior to the first cell cycle entry. As we will see, this lag may

be essential for the proliferative burst and for subsequent function of the clones, and the events surrounding these changes represent an emerging area of intense interest.

Preparing T cell metabolism for proliferation

In shifting from a small, resting cell to a rapidly cycling cell, a naïve lymphocyte effectively "reprograms" its metabolism, changing from a cell that relies on fatty acid oxidation (and some glycolysis), to one that engages robust aerobic glycolysis and glutaminolysis [2] (see Figure 1; here we focus on T lymphocytes, but similar events may well occur in activated B lymphocytes). This change relies on signaling events early in the activation process. For example, a hierarchical signaling cascade downstream of the cell surface receptors involved in MAPK (mitogen activated protein kinase)/ERK (extracellular signal-regulated kinase), PI3K (phosphoinositide 3-kinase)/Akt, mTOR (mammalian target of rapamycin) kinase and NFκB (nuclear factor-κB) pathways rapidly engages the expression of the transcription factor Myc, which, in turn, induces the expression of transporters for glucose and glutamine, and many of the enzymes involved in glycolysis, the pentose phosphate pathway, and glutaminolysis [2,3]. This reprogramming, thereby, directs nutrients to the production of nucleotides, lipids, amino acids, and other biosynthetic products needed for proliferation. Meanwhile, the activation of AKT and ERK facilitates post-translational surface expression of glucose

Figure I. Metabolic reprogramming in T lymphocytes



Following activation by recognition of antigen on antigen-presenting cells, T lymphocytes undergo metabolic reprogramming, shifting from FAO in the resting T cells to robust glycolysis and glutaminolysis as they prepare to enter the cell cycle. The associated changes are orchestrated at the mRNA level by the transcription factors Myc and ERR α . Activation of Akt and Erk facilitates post-translational surface expression of glucose transported Glut-I and glutamine transported SNAT2, respectively. As the cells proliferate they often differentiate into functional subtypes, including Treg, Th17, Th1 and Th2 cells. Such differentiation can also involve changes in metabolism, for example by the actions of HIF1 and GCN2 in Th17 cells. In addition, cells that persist in the form of memory T cells return to FAO to sustain energy, and this is inhibited by TORCI. Other events linking signaling to metabolism in T lymphocytes are outlined in the text. Abbreviations: ERR α , estrogen-related receptor α ; FAO, fatty acid oxidation; GCN2, general control nonrepressed 2; GLUTI, glucose transporter I; HIF1, hypoxia-inducible factor I; mTOR, mammalian target of rapamycin; mRNA, messenger RNA; SNAT2, system A neutral amino acid transporter 2; Th, T helper cell; TORC, TOR complex; Treg, regulatory T cell.

transporter Glut-1 and glutamine transporter SNAT2 (system A neutral amino acid transporter 2), respectively [4,5]. However, AKT is dispensable for increased glycolysis and proliferation in cytotoxic CD8 T cells; although these effects depend on PDK1 (phosphoinositide-dependent protein kinase-1), a well-known upstream regulator of AKT [6]. TORC (TOR complex) 1, a downstream signaling component of Akt, also plays a role in maintaining the metabolic gene transcriptome in naïve quiescent T cells [7]. Meanwhile, the suppression of the nuclear receptor LXR (liver X receptor) enhances cholesterol synthesis, an essential component of membranes [8], and the activation of an orphan steroid receptor, ERR α (estrogen-related receptor α), promotes lipid production, and perhaps mitochondrial biogenesis [9]. Coordinately, these events most likely prepare the activated T cells for their entry into their rapid cell cycle.

T cell metabolism and differentiation

As T lymphocytes begin to proliferate they also undergo differentiation into functional subsets in response to extracellular signals, and these subsets determine the nature of the immune response. CD4 T cells differentiate into Th (T helper) 1 cells that mediate responses to intracellular pathogens, Th2 cells that control responses to extracellular bacteria and helminthes, Th17 cells that are important in anti-fungal defense and inflammation, and induced Treg (regulatory T) cells that dampen immune responses. Of these, only the Treg cells rely on lipid oxidation as an energy source, and forcing proliferating T cells to utilize free fatty acids for energy tends to drive enhanced Treg differentiation [10]. In contrast, increased glycolysis is seen in differentiating Th17 cells, and this is a function of the transcription factor HIF1 (hypoxiainducible factor 1) [10,11]. Thus, damping of glycolysis with low dose 2-deoxyglucose inhibits Th17 and promotes Treg generation [11]. HIF1 also directly enhances ROR₇t activity and represses Foxp3 activity, producing a reciprocal increase in Th17 and decrease in iTreg differentiation [12]. Meanwhile, the choice between Th1, Th2 and Th17 differentiation is mediated in part by TORC1/2, the activation of which requires a surplus of intracellular amino acids pool; TORC1 promotes Th1 and Th17 differentiation, while TORC2 promotes Th2 differentiation [13]. In addition, the depletion of extracellular amino acids, either by amino acid catabolic enzymes such as IDO (indoleamine 2,3-dioxygenase), Arg I (arginase I) and asparaginase or by the small molecule halofuginone, results in the activation of the protein kinase GCN2 (general control nonrepressed 2) in T cells [14-17]. Consequently, Th17 differentiation is suppressed, whereas Treg development and T cell anergy are enhanced [14,18]. Each of these regulatory "nodes" (HIF1, TORC, GCN2) are responsive to metabolic status (e.g. oxygen availability, intracellular ATP

and amino acid pool), highlighting the connections between metabolism and T cell signaling.

Following the peak of proliferation and differentiation, there is a contraction phase as cells undergo apoptosis dependent on the pro-apoptotic proteins BIM and PUMA [19]. Cells destined to be memory T cells, responsible for enhanced immunity upon rechallenge, persist by employing fatty acid oxidation, the activity of which is associated with increased mitochondrial respiratory capacity and is negatively regulated by TORC1 activity [20-22]. The inhibition of TORC1 may require the function of the TSC (tuberous sclerosis protein) 1/2 complex, as cells lacking TSC1 do not generate immune memory [7].

Summary and future directions

We suspect that these studies merely "scratch the surface" of metabolic control of lymphocyte function. And of course, the immune response is not restricted to lymphocytes — the metabolic functions in cells of the innate immune system, including macrophages, dendritic cells, and others, are topics of ongoing investigation as well. Further, while much current work is directed at understanding how signaling pathways regulate metabolic changes, there are intriguing observations in these and other systems that support the converse; that is, that changes in metabolic substrates and products directly affect signaling. For example, the intracellular ATP and amino acid pools directly impact the activities of AMPK (AMP-activated protein kinase), TORC1 and GCN2 [14, 23, 24]. Further, enzymes in the metabolic pathways can also function in signaling. For example, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) has been implicated in the control of gene expression [25], and the glycolytic enzyme pyruvate kinase M2 isoform (PKM2) (expressed in cancers [26] and activated lymphocytes [2]) engages β-catenin signaling independently of Wnt [27]. We may intuit that these, and other critical enzymes, are likely to link metabolic status to signaling.

A great deal of excitement has followed the metabolic control of cancer in pointing the way to new therapies. The same may well apply to metabolic control of dysregulated autoimmune disease. These studies hold the promise for a renaissance in nutritional research, far beyond the "immune diet" fads, based on fundamental principles of the emerging connections between signaling pathways and metabolism.

Abbreviations

ERK, extra-cellular signal-regulated kinase; GCN2, general control nonrepressed 2; HIF1, hypoxia-inducible factor 1; Th, T helper cell; TORC, TOR complex; Treg, regulatory T; TSC, tuberous sclerosis protein.

Competing interests

The authors declare that they have no competing financial interests.

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