

Editorial overview: Metabolism of T cells: integrating nutrients, signals, and cell fate

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Nancie MacIver completed a BA in Mathematics at Johns Hopkins University before getting her MD degree, as well as a PhD in Immunology, from the Mayo Clinic. She then trained in Pediatrics and Pediatric Endocrinology at Duke University and thereafter joined the Duke faculty in 2009. Dr. MacIver is now an Associate Professor at the Duke School of Medicine with a primary appointment in the Department of Pediatrics and secondary appointments in the Department of Immunology and the Department of Pharmacology and Cancer Biology. Dr. MacIver's laboratory is studying the effects of large nutritional changes (both malnutrition and obesity) on T cell function and metabolism. These studies are applicable to many diseases, including diabetes, autoimmunity, and infection response, in which changes in nutritional status can influence immunity.

It is an exciting time in the field of immunometabolism. Over the last several years, there has been substantial progress in the understanding of how immune cell metabolism and function are influenced by one another, particularly in regards to lymphocytes. As T lymphocytes (T cells) are critical members of the immune system which orchestrate overall immune response through the production of cytokines and other immune factors, this special section of *Current Opinion in Immunology* highlights some of the key aspects of T cell metabolism. This includes new understanding about the utilization of distinct fuels to determine T cell differentiation and function, the response of T cells to both inadequate and overabundant nutrients, the role of T cell immunometabolism in diseases such as cancer, autoimmunity, and infection, and an improved understanding of the signaling pathways that regulate T cell metabolic changes at the molecular level. Altogether, this series of review articles provides a broad overview of the mechanisms by which T cell metabolism alters immunity in health and disease.

It is now well established that the metabolic properties of T cells are altered upon T cell activation and that different T cell subsets (e.g. naïve, effector, memory, regulatory) have distinct metabolic phenotypes. For the most part, naïve T cells utilize a mixed fuel metabolism dominated by oxidative phosphorylation to promote energy production for immune surveillance, whereas effector T cells (Teff) generally increase glucose and glutamine metabolism, with a predominant increase in aerobic glycolysis, in order to produce ATP quickly and to promote T cell growth and proliferation through the production of biosynthetic precursors [1]. Memory T cells (Tmem) and regulatory T cells (Treg), however, rely largely on oxidative phosphorylation and fatty acid oxidation to fuel immune surveillance and immune suppression, respectively [2–4].

There are, however, nuances in T cell metabolism amongst these broader categories of Teff, Tmem, and Treg. For example, while Teff cells such as Th1, Th2, and Th17 cells generally express high amounts of the glucose transporter Glut1, to promote glucose uptake and utilize a largely glycolytic metabolism, Treg cells usually express low levels of Glut1 and generally utilize oxidative metabolism to fuel suppressive function [2,5]. When cultured *in vitro*, however, Treg cells were shown to engage in both glycolysis and fatty acid oxidation to enhance proliferation, and conditions such as acute infection or inflammation have been shown to provide signals that increase Treg Glut1 expression and glycolytic metabolism such that Treg become more proliferative but less suppressive [6]. Likewise, Teff cells vary in their metabolic programs. In the review by Kidani *et al.*, the authors review recent studies demonstrating that the cholesterol and fatty

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acid synthesis pathways promote ROR γ activity and IL-17 production in Th17 cells, specifically; however, why fluxes through lipid synthetic pathways promote Th17 differentiation remains unknown.

Despite the findings that T cells alter their metabolic state upon activation, it is not entirely clear how altered nutrient availability and the overall metabolic state of the organism influence T cell function and response to infection. The review by [Balmer *et al.*](#) describes how infections disrupt homeostasis and lead to a switch toward catabolic metabolism at the organismal level. That, in turn, leads to increased systemic availability of glucose, fatty acids, and ketone bodies which may disturb immune cell metabolism. For example, increased glucose availability is likely to promote T cell activation in an acute infection response through increased glycolytic metabolism. Increased availability of fatty acids may be utilized by T cells for fuel, for storage of lipid droplets, and for incorporation into membrane lipid rafts. Increased ketone bodies and acetate may be metabolized into acetyl-coA to fuel the TCA cycle or to generate acetyl-groups for increased acetylation of proteins. Moreover, acetylation of the glycolytic enzyme Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) has been shown to increase GAPDH activity as well as promote glycolysis [7].

Infection response in obesity, however, is likewise disrupted through altered availability of nutrients systemically. As [Green *et al.*](#) discuss, the obesity epidemic in the developed world has broad implications for immune response through effects on T cell metabolism and function. Obesity has been shown to impair immune response to select infections such as H1N1 and seasonal influenza by altering and impairing both B cell and T cell response. Moreover, diet-induced obese and genetically obese mice displayed altered metabolomics profiles in many tissues following infection with influenza, in comparison to infected lean mice [8]. The mechanism by which T cell function and infection response are altered in obesity is not entirely clear, yet there is evidence that these changes are downstream to alterations in nutrients, cytokines, and hormones seen in obesity. Indeed the hormone leptin is increased in obesity and has been shown to promote T_H17 cell response by promoting T_H17 glycolytic metabolism upon activation and driving the production of inflammatory cytokines IFN- γ and IL-17 [9–11]. Infection response in obesity is, therefore, likely to result in altered T cell metabolism and impaired T cell response, in part, by promoting T cell inflammation and reducing anti-inflammatory immune surveillance and memory formation.

T cell metabolism also plays a key role in immune response in both autoimmune disease and cancer immunosurveillance. The review by [Weyand *et al.*](#) highlights the metabolic abnormalities of T cells in rheumatoid arthritis, characterized by a diversion of glucose metabolism toward a synthetic/proliferative phenotype, shifting T cells into a low energy state, diverting ATP production toward the pentose phosphate pathway, and thereby increasing NADPH while consuming reactive oxygen species (ROS). This ATP-low, NADPH-high, ROS-low state of T cells drives T cell proliferation and promotes differentiation into pro-inflammatory Th1 and Th17 subsets [12]. At the same time, these energy-deprived T cells in rheumatoid arthritis lose DNA repair abilities, accumulate telomeric damage, and enter premature senescence [13]. On the other hand, macrophages in rheumatoid arthritis are characterized by mitochondrial stress, increased glucose uptake and increased glycolytic activity, and over-production of the inflammatory cytokine IL-6, altogether predisposing toward an inflammatory state [14]. In the field of cancer immunology, [Ho *et al.*](#) describe how

metabolic stresses in the tumor microenvironment (nutrient deprivation, hypoxia, acidosis, etc.) lead to altered T cell metabolism and decreased T cell anti-tumor immunity. Here, the authors suggest that manipulation of the T cell metabolic state to promote tumor-specific memory T cells may be a useful treatment to improve T cell anti-tumor response. Likewise, [Sukumar *et al.*](#) also describe recent work demonstrating that modulation of T cell metabolism may improve T cell anti-tumor immunity. In this review, the key metabolic properties of anti-cancer T cells are described as dynamic, requiring metabolites to promote both T cell effector function and long-term survival. T cells with low mitochondrial membrane potential had phenotypes that promoted memory T cell formation, whereas T cells with high mitochondrial membrane potential were more glycolytic with increased effector gene expression [15]. The authors propose a model for anti-tumor immunity where cells are selected for high metabolic activity during *in vitro* expansion and priming, in order to assume an effector phenotype, followed by a selection of T cells with constrained metabolic activity when applied to the tumor site, in order to promote long-lasting cell survival and persistent anti-tumor immune response.

It is important to note that many of the factors that influence T cell metabolism (nutrients, cytokines, growth factors, etc.) do so through regulation of key signaling proteins, including the mammalian target of rapamycin (mTOR) and AMPK-activated protein kinase (AMPK). AMPK is a metabolic regulator that senses changes in cellular energy status and functions to maintain energy balance through its ability to promote ATP-producing pathways (e.g. glycolysis, fatty acid oxidation) while inhibiting ATP-consuming pathways (e.g. synthesis of macromolecules such as proteins and fatty acids). [Ma *et al.*](#) describe recent work highlighting the role of AMPK in T cells, including the ability of AMPK to respond to changes in T cell nutrient availability, as well as how AMPK influences T cell metabolism to alter Tmem development, T_{eff} cytokine production, and T cell tumor response. Additionally, activation of AMPK negatively regulates mTOR complex 1 (mTORC1) activity in T cells and reduces protein translation. [Zeng *et al.*](#) review the role of mTOR in the differentiation and function of T_{reg}, T_{mem}, and T_{eff} cells, including the unique population of T follicular helper (T_{fh}) cells which influence B cell differentiation and production. T cell signaling through T cell receptors, costimulatory receptors, and cytokine receptors all activate the PI3K/Akt/mTOR pathway to promote metabolic reprogramming and favor cell growth and proliferation. As the authors of this review discuss, the role that mTOR plays is distinct in various T cell subsets, and therefore understanding the regulation of mTOR in T cells is of critical importance. This is complex, as multiple upstream signals influence mTOR signaling and these signals are contextually dependent.

Interestingly, recent studies have shown that during CD8⁺ T cell proliferation, there is an asymmetric segregation of metabolic regulators which dictate cell fate. During T cell activation and division, the cell most proximal to the antigen presenting cell (APC) becomes a short-lived T_{eff} cell characterized by increased expression of mTORC1 and the pro-glycolytic transcription factor Myc, whereas the cell more distal from the APC has low mTORC1 and Myc levels and differentiates into a T_{mem} cell [16,17].

Lastly, the review by [Patel *et al.*](#) suggests approaches by which we may use the above lessons to target T cell metabolism and alter the course of disease. Several drugs have been identified that may target aspects of T cell metabolism. For example, the drug rapamycin can be used to inhibit mTOR activity and promote T_{reg} generation and T_{eff} anergy while enhancing T_{mem} development. Alternatively, targeting of the mTORC1 inhibitory protein TSC2 may enhance mTORC1 activity and increase T_{eff} function. Modulation of amino acid metabolism may alter T_{eff}/T_{reg} differentiation; as one example of this approach, use of the glutamine antagonist 6-Diazo-5-oxo-L-norleucine (DON) has been shown to disrupt T cell response. The glycolytic inhibitor 2-deoxyglucose (2-DG) has been tested as a therapy to decrease inflammation in mouse models of inflammatory disease, and was found to decrease the Th17/T_{reg} ratio. Other approaches have targeted glucose-derived pyruvate metabolism, fatty acid metabolism, and mitochondrial function. When used alone or together [18], these drugs can selectively alter T cell subsets in ways that may be therapeutically useful in the treatment of a variety of diseases and conditions including autoimmunity, organ or graft rejection, anti-tumor immunity, and infection response.

Altogether, this series of review papers highlights some of the important work done over the last 5–10 years in the field of T cell metabolism. As is demonstrated in the above reviews, T cells are comprised of a complex group of subsets with varying functional and metabolic phenotypes. Better understanding of these distinct T cell subset properties can enhance our understanding of T cell metabolism and function in health and aid us in the development of immunometabolic targets for the treatment of disease.

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