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Tweaking T Cell Bioenergetics

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Introduction

The functional status of lymphocytes is tightly linked to metabolism as glycolysis and mitochondrial respiration supply lymphocyte activation with necessary intermediates. It is currently accepted that resting lymphocytes such as naïve or memory T cells utilize oxidative phosphorylation for ATP production. Following activation, metabolism in T cells switches from catabolic to aerobic anabolic glycolysis and glutaminolysis. This transition is similar to metabolic shift in tumor cells, described as the Warburg effect [1,2]. In Warburg-shifted activated T cells, glucose transport is upregulated leading to an overall rise in intracellular glucose levels that result in high production of pyruvate. Further, pyruvate is converted into lactate and secreted out of cells. Also, glycolytic reactions are involved in multiple metabolic pathways, such as pentose phosphate, responsible for synthesis of nucleotides and lipids necessary for the generation of daughter cells during cell divisions. At the same time, Fatty Acid β-Oxidation (FAO), catabolic metabolism of fatty acids, is down-modulated in activated T cells. Such T cell metabolic reprogramming is coordinated by engaged T Cell Receptor (TCR)-triggered intracellular pathways, for example, Akt/mTOR axis [1,2].

Lymphocyte differentiation into various subsets induces radical changes in requirements of lymphocytes for their persistence and survival. Upon activation, $CD4^+$ T cells differentiate into several subsets such as Th1, Th2, Th17, and Treg. These Th subsets are involved in the regulation of inflammation including chronic inflammatory processes [3]. During the development, activation and differentiation of CD8+ T cells, cell surface free thiols are upregulated following receptor ligation and reactive oxygen intermediates production during infection to prevent overoxidation of surface proteins [4]. These differentiation paths are also dependent on environmental factors, such as polarizing cytokines, and rely heavily on metabolic status. For example, activated T cells lose their dependence of IL-7 and instead require IL-2 and IL-15 that promote mitochondrial biogenesis. Similarly, fatty acid β-oxidation favors differentiation of Treg cells while Th17 cells utilize predominantly glycolysis [5].

Although the role of mitochondria in T cell death was known for a long time, its function in T cell activation was not clear until recently. It is well known that inner mitochondrial membrane carries positive electric charge. This forms mitochondrial membrane potential (MMP) by the directed transport of protons from matrix into the intermembrane space during oxidation of respiratory substrates. In early studies, it has been established that upon T cell activation mitochondria undergoes hyperpolarization with elevated MMP [6,7]. This alteration in MMP is accompanied by a rise in ROS production and serves as a checkpoint for T cell death [8]. Dramatic changes in MMP and ATP production were described in T cells from patients with systemic lupus erythematosus [8,9] and with HIV-1 infection [10]. These studies proposed the important role of mitochondria in lymphocyte activation.

Although, in activated T cells, glycolysis predominate mitochondria in terms of ATP synthesis, mitochondrion still plays a major role in the regulation of intracellular signaling via production of Reactive Oxygen Species (ROS). Indeed, ROS maintains Nuclear Factor of Activated T cells (NFAT)-dependent stimulation of T cells including IL-2 production and antigen-specific expansion [11]. At least two mitochondrial sources are responsible for superoxide anion O_2- production in activated T cells: glycerol-3 phosphate Dehydrogenase and complexes I and III of the respiratory chain [11-13]. Further, O_2- is converted into hydrogen peroxide (H_2O_2) by mitochondrial superoxide dismutase; H_2O_2 diffuses into the cytosolic compartment where it participates in activation of NFAT [14]. Production of O_2- by respiratory chain in activated T cells, like in other cell types, is mediated by mitochondrial calcium uptake mechanisms, thus coupling T cell receptor-driven cytosolic Ca^{2+} rise with Ca^{2+}-dependent ROS production in mitochondria [11].

In addition, an important role was shown for mitochondria in memory T cells. For example, IL-15 cytokine, which is crucial for T cell memory, promotes mitochondrial biogenesis, and up-regulation of Carnitine Palmitoyl Transferase CPT1, a key rate-limiting enzyme involved in fatty acid oxidation in mitochondria. These changes lead to an elevation in mitochondrial spare respiratory capacity, thereby increasing T cell responsiveness to various stimuli such as repeated antigen challenge [2]. Consequently, memory T cells upon reactivation respond faster to stimuli than naïve T cells [15]. Effector memory T cells lacking lymph node homing receptors CCR7 and CD62L are capable of screening antigens in non-lymphoid tissues have higher migratory potential, which is associated with elevated expression of mitochondrial metabolic genes including uncoupling proteins 2 and 3 [16].

Based on the important role of bioenergetics in the development of T cell immunity, it is logical to propose that bioenergetics manipulation will have major bearing on the success of T cell-based immunotherapy. Identification of molecular targets that can intercept mitochondrial metabolism or glycolytic switch might influence the fate of T cells, thus giving rise to new tools for refining anti-tumor immune response. An approach for the treatment of graft-versus-host disease has been proposed based on the use of Bz-423, a small-molecule inhibitor of mitochondrial ATP synthase; Blocking of latter leads to hyperpolarization of MMP, increased ROS production and induction of apoptosis in alloreactive T cells [5,17]. The role of mitochondrial ROS in the activation of T cells [11-13] might give rise to another therapeutic strategy, i.e. treatment with antioxidants. Indeed, a number of mitochondria-targeted antioxidants were recently characterized such as Mito vitamin E, mitotempo, mitoQ etc. It was shown that

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mitochondrial ROS stimulates HIF-1 mediated glycolysis as well as Akt and Erk activation, thereby supporting cell growth and reducing cell death [18]. Thus, scavenging of ROS in mitochondria would affect metabolic reprogramming and fate of T cells.

Attenuation of glycolysis by hexokinase inhibitor, 2-DeoxyGlucose (2-DG), was shown to down-modulate Th17 differentiation thus decreasing disease severity in experimental autoimmune encephalitis [19]. Furthermore, 2-DG enhanced $CD8^+$ T cell memory formation due to up-regulation of transcription factors Tcf7 and Lef1 defining memory T cell stemness. As a result, tumor-bearing mice treated with 2-DG displayed more lymphocyte infiltration, cytokine production and tumor rejection [20]. Another pharmacological agent, etomoxir, inhibits FAO in Treg cells-natural attenuators of anti-tumor T cell immunity. This makes etomoxir a potential drug to enhance cancer immunotherapy [5].

New strategies to target metabolic changes in T cells, for selective immunomodulation, will be complemented by the rapidly emerging data in the near future. Although the full picture of metabolic changes in T cells following activation is still far from completely understood, existing results give opportunities for designing new strategies combining metabolism-based approaches with classical immunotherapeutic regimens.

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