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Original Article

Metabolic reprogramming and apoptosis sensitivity: Defining the contours of a T cell response

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ABSTRACT

An effective adaptive immune response hinges on the rapid clonal expansion of T cells in response to antigen. The sensitivity of these T cells to programmed cell death (i.e. apoptosis) is carefully calibrated at various stages to ensure a robust yet measured reaction that resolves without inflicting unintended damage to host tissues. To meet bioenergetic demands associated with vigorous proliferation, acquisition of effector functions, and memory formation, T cells also undergo dynamic changes in their metabolism at every stage of this response. In this review, we focus on relatively recent studies that illuminate intimate links between metabolic programs and apoptosis sensitivity in T cells. We then examine how these connections ultimately influence T cell survival and function within the metabolically taxing environs of the tumor microenvironment.

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Introduction

The adaptive immune response is intricately linked to the cellular metabolism of lymphocytes. Many recent studies have underscored the importance of dynamic metabolic reprogramming over the course of the immune response [1,2]. Basic properties associated with effector T and B cells, including proliferation, differentiation, migration, and effector functions (e.g. cytokine production), have different metabolic demands and therefore require flexibility in metabolic programming. This metabolic adaptability is also vital for responding T cells that encounter challenging anatomical niches, including the tumor microenvironment or certain sites of infection such as *Mycobacterium tuberculosis* (*Mtb*)-induced granulomas.

Although advances in our understanding of both immunology and cancer biology have empowered progress in immunometabolism research, the extent to which changes in metabolic programs shape the T cell memory response requires further elucidation. Moreover, the magnitude and potency of any T cell response is also ultimately shaped by the sensitivity of those T cells to programmed cell death at various phases. However, the question of how cellular metabolism contributes to T cell apoptosis during the immune response has only just started to be investigated.

As the adaptive immune response unfolds, responding T cells become sensitized to various apoptotic signals in order to maintain immune homeostasis. Following activation and several days of clonal expansion, effector T cells become increasingly sensitive to apoptosis in the presence of cytokines [3,4]. Specifically, at the peak of an adaptive immune response when antigen is still abundant, T cells are subject to a “negative feedback” apoptotic mechanism mediated by restimulation of the T cell receptor (TCR) [5]. This TCR-induced apoptosis, also known as restimulation-induced cell death (RICD), constrains the magnitude of effector T cell proliferation to prevent damaging immunopathology [6]. As pathogens and/or transformed cells are eliminated from the system, antigens are cleared and cytokines such as interleukin-2 (IL-2) that promote T

Abbreviations: AICD, Activation-induced cell death; Bcl-2, B cell lymphoma 2; BH3, Bcl-2 domain homology 3; CM, Central memory; COX, Cytochrome *c* oxidase; CWID, Cytokine withdrawal-induced death; EM, Effector memory; FasL, Fas ligand; FAO, Fatty acid oxidation; FASN, Fatty acid synthase; IL-2, Interleukin-2; IL-7, Interleukin-7; Mtb, *Mycobacterium tuberculosis*; OXPHOS, Oxidative phosphorylation; PPP, Pentose phosphate pathway; PD-1, Programmed death-1; ROS, Reactive oxygen species; Tregs, Regulatory T cells; RICD, Restimulation-induced cell death; SLAM, Signaling lymphocyte activation molecule; SRC, Spare respiratory capacity; T-ALL, T cell acute lymphoblastic leukemia; TCR, T cell receptor; TCA cycle, Tricarboxylic acid cycle; TIL, Tumor infiltrating lymphocytes; XLP-1, X-linked lymphoproliferative disease.

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cell expansion also decline. Waning cytokines and growth factors induce an intrinsic apoptosis program known as cytokine withdrawal-induced death (CWID), also referred to as activated cell autonomous death (ACAD) [7,8]. CWID culls most of the effector T cell population during this contraction phase, leaving only a small pool of T cells that persist as memory T cells. Both RICD and CWID are critical for maintaining immune homeostasis; therefore, this review will focus on how these death programs are influenced by T cell metabolism (Fig. 1).

Changes in T cell metabolism impact apoptosis sensitivity

Intricate links between metabolism and apoptosis have been detailed in various eukaryotic cell types, often with mitochondria as the central players. Studies establishing connections between apoptosis and glycolysis, the tricarboxylic acid cycle (TCA cycle), and the pentose phosphate pathway (PPP) have been explored in the context of cancer, diabetes, and neurodegenerative disorders [9]. With the recent explosion of research into immunometabolism, particularly in T cells, links to apoptosis sensitivity are just now garnering attention.

Apoptosis is a particularly important regulator of immune homeostasis because either a paucity or over accumulation of lymphocytes can have detrimental consequences, giving rise to immunodeficiency or autoimmunity, respectively. If control is lost through apoptotic defects, an overactive immune response to pathogens can pose danger to the host in the form of lymphoproliferation and immunopathological damage [6,10]. Furthermore, chronically activated T and B lymphocytes undergoing rapid proliferation are at increased risk of sustaining mutations, which can contribute to the development of lymphoma [8]. Alternatively, premature or excessive apoptosis could result in a lackluster T cell response that leaves the host susceptible to infectious diseases and/or cancer. Overall, T cell apoptosis sensitivity is carefully calibrated over the course of an adaptive immune response to ensure both effective clearance of pathogen and disposal of activated cells that are no longer needed and potentially dangerous to the host if left unchecked.

Naïve T cells are metabolically quiescent, relying largely on oxidative phosphorylation (OXPHOS) for ATP generation prior to antigen engagement [11]. Upon TCR/CD28 stimulation, activated T cells upregulate their anabolic metabolism to meet higher demands required for energy production, rapid cell proliferation and acquisition of effector functions. This burst of activity is associated with rapid uptake of nutrients like glucose and amino acids that jumpstart a profound increase in both glycolysis and OXPHOS, although the increase in glycolysis is much larger [12,13]. Activated T cells upregulate cell surface expression of the glucose transporter Glut1, which is dependent on CD28 costimulation [13,14]. Glut1-mediated glucose import and subsequent processing through the glycolytic machinery provides an abundant carbon source for building macromolecules for clonal expansion, as well as ATP. This shift to glucose dependency can also protect T cells from intrinsic apoptotic stimuli, such as osmotic stress in mouse T cell lymphomas [15]. Similarly, the viability of proliferating Jurkat and primary human T cells in culture decreases as glucose availability is limited, highlighting the importance of glucose as a metabolic substrate for activated T cell survival [13,16]. Increased T cell death during glucose deprivation was linked to mitochondrial integrity, which is normally controlled by a balance of pro- and anti-apoptotic B cell lymphoma 2 (Bcl-2) family proteins. Specifically, increased expression of pro-apoptotic Bcl-2 domain homology 3 (BH3)-only proteins such as Bim, Puma and Noxa can initiate programmed cell death by binding and counteracting the function of anti-apoptotic Bcl-2, Bcl-xL, and Mcl-1 proteins [17]. In fact, knockdown of Noxa improved survival of activated T cells experiencing glucose limitation [16], establishing a specific role for Noxa in eliminating glucose-starved T cells. The pro-survival effect of cytokines like IL-2 and IL-7 for expanding T cells is also linked to enhanced glucose influx. Specifically, IL-7-mediated survival conferred by STAT5-dependent Akt activation was partly dependent on increased Glut-1 expression and glucose uptake; IL-7 alone was insufficient to rescue cells from apoptosis in glucose-limiting conditions [18].

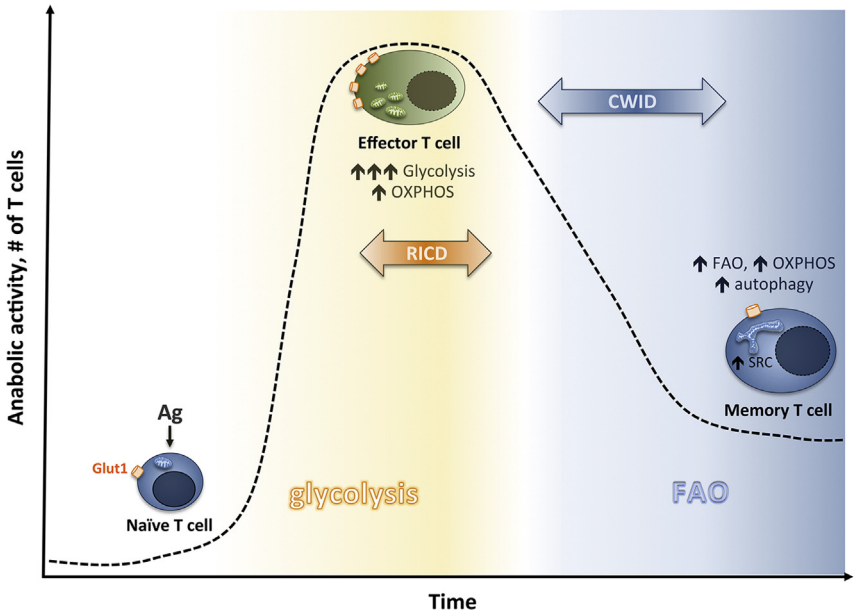

Fig. 1. Sensitivity to critical apoptosis pathways correlates with metabolic reprogramming over the course of the T cell response. Naïve T cells exist in a metabolically quiescent state until antigen (Ag stimulation), which triggers increased Glut1-mediated glucose uptake and an abrupt increase in aerobic glycolysis (as well as OXPHOS). Enhanced glycolysis sensitizes effector T cells to RICD by enabling TCR-induced FasL induction upon Ag re-encounter. As Ag is cleared, most effector T cells are culled through CWID. Those T cells that persist into the memory pool likely escape both RICD and CWID by inducing protective autophagy and turning off glycolysis in favor of FAO-direct OXPHOS. This metabolic switch returns memory T cells to a more quiescent state, "primed" for rapid recall responses via increased spare respiratory capacity.