Viewpoint

Angry, Hungry T-Cells: How Are T-Cell Responses Induced in Low Nutrient Conditions?

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ABSTRACT

Upon activation, T-cells increase the uptake of glucose and glutamine to build the constituents of proliferating effectors. However, tumor and infected cells compete for the same nutrients. Several observations are consistently indicating that activated T-cells overcome this situation by engaging catabolic pathways. Here I discuss how these observations are reconciled with T-cells' need of anabolic processes during activation.

KEYWORDS: fatty acid oxidation; autophagy; AMPK; nutrient starvation; nutrient deficiency; T-cells

According to current paradigms, resting T-cells, once activated, shift from a catabolic to an anabolic metabolism which is necessary to sustain their growth, proliferation and effector functions. This energetic switch is controlled by mTOR, whose activation leads to induction of downstream processes including glutaminolysis and aerobic glycolysis—two pathways that provide intermediates needed for the biosynthesis of new nucleotides, amino acids and fatty acids (FA) for proliferating T-cells. To fuel this biosynthetic machinery, T-cells cannot just rely on internal nutrient stores. For instance, upon T-cell activation, new FAs are supplied for the cell not only via upregulation of FA synthesis (FAS) and lysis of triacylglycerols, but also by the cell's increased uptake of extracellular FAs [1,2]. Similarly, both glucose and glutamine intake are induced upon TCR triggering.

However, T-cell responses are deeply influenced by both the organism nutritional status and the local microenvironment. Protective immunity is indeed disrupted in both undernourished and overnourished individuals due to changes in circulating hormones and metabolites [3–5], a phenomenon exacerbated by the infections themselves, with further negative consequences on disease control [6,7]. In addition, T-cell responses take place at effector sites usually limited in nutrients [8,9]. For instance, infections often alter levels of certain metabolites in infected cells, in other immune cells interacting with lymphocytes or even systemically [7,10–14]. Additionally, at both infection and tumor sites, a huge competition for glucose and glutamine exists [8], and a high glycolytic rate in cancer cells has been shown to correlate with the low effector functions of intratumor T-cells [15]. The tumor micro-

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environment is also poor of co-stimulatory molecules, further preventing the metabolic switch in activated T-cells [16]. T-cells have shown to cope with these situations by shifting from glycolysis to glutaminolysis [14] and vice versa [17]. Conversely, tumor cells may not share the same metabolic plasticity. For instance, glycolysis inhibition blocks lactate secretion by tumor cells and augments T-cell infiltration and effector functions as well the effectiveness of checkpoint inhibitors [18]. Effector T-cells react to glucose withdrawal by boosting glutamine metabolism for ATP generation—a process controlled by the adenosine monophosphate-activated protein kinase (AMPK), whose activity is regulated by the AMP/ATP ratio [14]. Similarly, while glutaminolysis blocking disables tumor cells, it may improve T-cell functionality [17] by prompting the usage of FAs and glucose metabolism derivatives to fuel the tricarboxylic acid cycle and generate ATP [17]. High ATP levels will then down-modulate the AMPK activity [17] finally enabling the initiation of anabolic processes (which are inhibited by AMPK). Therefore, T cells activated in low nutrient conditions seem to alternate cycles of ATP generation (supported by AMPK) with cycles of anabolic processes (requiring AMPK inactivation).

Calorie restriction (CR) represents an interesting model to study T-cell behavior in low nutrient settings, as it enhances the responsiveness of T-cells and reduces their terminal differentiation. In addition, CR induces autophagy [19,20] and prompts T-cells to migrate into the bone marrow (BM), where they survive in a lipid-rich environment [21–24]. As CR affects both metabolite [25] and hormone [21] levels, the exact contribution of each single factor is difficult to define. Nevertheless, lipid usage and autophagy seem to be important pathways exploited by T-cells under CR. Notably, the induction of autophagy and lipid catabolism in activated T-cells may seem counter-intuitive, as both pathways are inhibited by mTOR. Autophagy induction is crucial for the survival of cells (including lymphocytes) during starvation or hypoxia [26–28] and for the maintenance of memory T-cells [26,27,29]. However, some recent publications have also described a role for autophagy in the stimulation of early-differentiated $CD8^+$ T-cells, where it is induced simultaneously with mTOR triggering [30,31]. More than that, mTOR activity itself seems supported by autophagosomes [32]. In this respect, an interesting observation comes from the comparison of naïve with central memory T-cells. Both subsets reside in secondary lymphoid organs and have minimal energetic requirements. However, naïve T-cells display a lower basal nutrient uptake and thus suffer, *de facto*, from a limited access to nutrients. Nonetheless, they can compensate for this disadvantage by upregulating both mTOR and autophagy to levels higher than those of central memory T-cells [31]. Therefore, autophagy seems to provide additional energy to T-cells activated during nutrient deficiency. Similarly, FAO is considered the central energy source for resting T-cells [33], while TCR stimulation induces its opposite pathway, FAS. However, the induction of FAO during the priming of naïve $CD8^+$ T-cell has been shown

to boost the functionality of new effectors without altering their proliferation rate [31], especially during nutrient deficiency within tumors [34–36]. Indeed, it has been demonstrated in both tumor and persistent infection models that T-cells activated in a glucose-deprived and hypoxic microenvironment show enhanced expression of inhibitory checkpoints [34,37] associated with a reduced glycolysis and compensated by an increased FAO [34,38]. While the use of immune checkpoint blockers may in part reprogram T-cell metabolism [37,38], the simultaneous activation of FAO (through drugs) helps T-cells to overcome their reliance on glucose and improves their effector functions and the effectiveness of anti-PD-1 therapy [34–36]. These pieces of evidence show that metabolic pathways generally used by resting T-cells may be important upon activation to overcome poor nutrient availability. Nonetheless, it is unclear how proliferating T-cells, which exploit an mTOR-dependent anabolic metabolism, may be sustained by autophagy and FAO (which are rather inhibited by mTOR). The answer may derive in part from the observation of the bioenergetic features of resting memory T-cells. Indeed, despite the fact that they are considered highly reliant on FAO, their FA uptake is usually low. Quiescent T-cells are thought to themselves synthesize the FAs that will then be oxidized, alternating FAS and FAO [39]. FAS utilizes ATP, increasing the AMP/ATP ratio and inducing AMPK activity. AMPK then inhibits FAS and stimulates FAO, which generates ATP. This decreases the AMP/ATP ratio, switching off AMPK so that FAS may begin again, We cannot exclude that a similar cycle may occur during nutrient deprivation and that, in this way, AMPK may also control the mTOR/autophagy balance (e.g., alternating cycles of AMPK and mTOR activity).

In conclusion, several independent observations highlight that T-cells may meet their energetic demand during nutrient deficiency by using AMPK-controlled pathways such as autophagy and FAO [40]. However, to reconcile their metabolic requirements and growth needs, T-cells may be forced to alternate catabolic and anabolic processes in order to make up for the lack of biomolecules and construct the building blocks of proliferating cells, respectively. To finally translate immunometabolic studies into clinical practices, it will be crucial to finely dissect the kinetics of the different metabolic pathways engaged by T-cells in low nutrient settings (e.g., during infections, in tissues, during systemic metabolic alterations). Indeed, so far it is not yet clear whether the shift toward catabolic processes, enforced in nutrient-deprived settings, should be favored, to limit the competition for glucose [34–36], or should be rather counteracted, to improve T-cell glycolytic rate [41,42]. In addition, we are still far from knowing how different T-cell subpopulations react to poor biomolecule availability, and this constitutes a great limitation considering the huge amount of conditions, such as infections and age, that unbalance the proportion of early and late differentiated T-cell subsets [43–46]. It is therefore important that, when considering the use of molecules capable of affecting T-cell metabolism, such

immunotherapeutic strategies should not desynchronize the bioenergetic processes of lymphocytes and thus undermine their capability to overcome nutrient deprivation.

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