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Highlights

COMMENTARY:

Staying alive – naïve CD4$^+$ T cell homeostasis

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The immune system must maintain a broad repertoire of naïve T cells in order to respond to the diverse range of pathogens that it will encounter over the course of a lifetime. Although it is known that contact with IL-7 is crucial for the survival of naïve T cells, the precise intracellular signals that mediate its effects remain obscure. An article in this issue of the *European Journal of Immunology* has found that IL-7 requires the coordinated action of multiple pathways to maintain naïve CD4$^+$ T cells.

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Introduction

Naïve T cells develop in the thymus and migrate to the peripheral lymphoid compartments throughout life. Before discussing the homeostatic mechanisms that control T cell numbers and survival, it is worth considering the factors that influence their development in the thymus. Bone-marrow-derived precursors are dependent upon IL-7 signaling for survival while they rearrange their TCR β genes which, if successful, leads to their expansion into immature CD4$^+$CD8$^+$ thymocytes [1]. These precursors now rearrange their TCR α genes in an attempt to produce a TCR that can interact with self-peptide MHC complexes (sp-MHC) with enough affinity to ensure their positive selection and survival; however, immature thymocytes are also subject to negative selection, which causes the deletion of clones whose TCR has too high affinity for sp-MHC. Only a very small proportion of thymocytes possess a TCR whose affinity for sp-MHC falls in the narrow range that allows it to survive both positive and negative selection and leave the thymus for the periphery. This low but significant affinity for sp-MHC is important as it provides survival signals through the TCR for naïve CD4$^+$ T cells in the periphery (reviewed in [2]).

The role of IL-7 in supporting naïve T cell homeostasis was not initially realized largely due to the essential role it plays in early T cell development [3]. The first clue that IL-7 was important for the homeostasis of naïve T cells was that it could prevent them from dying *in vitro* [4]. Furthermore, treatment of normal mice with IL-7-depleting antibodies caused a decrease in overall naïve T cell numbers [5, 6]. The crucial requirement for IL-7 under *in vivo* conditions was then demonstrated by the finding that naïve T cells transferred to IL-7-deficient hosts had a dramatically abbreviated lifespan [7, 8]. In addition, IL-7 was found to be essential for naïve T cells to undergo spontaneous homeostatic proliferation in response to severe lymphopenia. Thus leading to the establishment of the current paradigm that IL-7 at normal physiological conditions supports naïve T cell survival, but induces homeostatic proliferation at elevated levels (reviewed in [2]).

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Abbreviations: **γc:** common gamma chain · **M1:** Marylin TCR transgenic · **sp-MHC:** self-peptide MHC complexes

IL-7 is a member of a family of cytokines that all share a common receptor γ chain (γc) which also includes IL-2, IL-4, IL-9, IL-15 and IL-21. IL-7 binding to the γc and its unique α chain, IL-7Rα (CD127), activates multiple signal transduction pathways including Janus kinase (JAK)1 and JAK3, MAPK, src kinases, PI(3)-K and the PKB (or Akt) protein kinase family (reviewed in [9]). The anti-apoptotic protein Bcl-2 is the best known downstream target of IL-7-driven γc signaling and the up-regulation of this protein by IL-7 is one of its major effects on thymocyte development [10]. In fact, the over-expression of Bcl-2 alone largely restores naïve T cell numbers in IL-7-deficient mice [11]; however, prevention of cell death by Bcl-2 is only half the story. IL-7 signals to T cells also maintain cell size and promote glucose and protein metabolism [12]. This is important as reduction in cell size, increased protein degradation coupled with decreased protein synthesis, and reduced glucose metabolism can all lead to death-by-neglect [13]. In particular, reduced glucose metabolism leads to the loss of substrates that mitochondria need to maintain their inner membrane electrochemical potential, a crucial indicator of cell viability. The PKB protein kinase family appears to be the best candidate for mediating these trophic effects of IL-7 as a considerable body of literature has documented the ability of PKB signaling to promote both glucose metabolism and protein synthesis (reviewed in [13]).

γc cytokines and naïve CD4$^+$ T cell homeostasis

One of the key steps for understanding naïve T cell homeostasis is to identify the precise downstream signaling pathways that mediate the effects of IL-7. In this issue of the *European Journal of Immunology*, Masse *et al.* [14] addressed this question by selectively restoring Bcl-2 and/or PKB signaling to naïve CD4$^+$ T cells that are γc-deficient and therefore cannot receive survival signals from any of the γc cytokines. This has not been addressed previously due to the fact that only very minute numbers of CD4$^+$ T cells are generated in γc$^-$ mice and most of these cells have a memory phenotype [15]. To avoid this problem, the present study uses γc$^-$ mice expressing a TCR transgene, the Marylin (M1) TCR specific for the male antigen HY Dby, which allows enhanced generation of naïve CD4$^+$ T cells. On a Rag2-deficient background, the mature M1 CD4 T cells that develop in both γc$^+$ and γc$^-$ hosts display a naïve CD44^{lo}CD62L^{hi} phenotype [16]; however, γc$^-$ M1 CD4$^+$ naïve T cells are 200-fold reduced in number compared to their γc$^+$ counterparts. The γc$^-$ cells are also smaller in size with a decreased mitochondrial membrane potential than normal cells, suggesting that these cells have poor cellular metabolism. These results extend previous observations made *in vitro* [12].

Masse *et al.* [14] tested which of these defects of γc$^-$ M1 CD4$^+$ naïve T cells could be corrected by Bcl-2. The Tg overexpression of Bcl-2 restored the numbers of γc$^-$ M1 CD4$^+$ naïve T cells to near normal levels and corrected the defect in their mitochondrial potential. These results indicate that Bcl-2 alone can correct most of the survival deficiency of these cells; however, Bcl-2 Tg γc$^-$ M1 CD4$^+$ naïve T cells were still smaller than normal in terms of their cell size. The authors also present evidence that overexpression of Bcl-2 failed to prevent a global reduction in ribosomal protein transcripts. Collectively, these results suggest that Bcl-2 Tg γc$^-$ M1 CD4$^+$ naïve T cells still possess defective cellular metabolism, indicating that they would likely respond poorly to mitogenic or trophic signals. Indeed, this defect may partially explain the decreased response of these cells observed after antigen stimulation *in vitro* [14]. These results raised the question of whether normal cellular metabolism could be restored in γc$^-$ M1 CD4$^+$ naïve T cells by PKB activity alone or in combination with Bcl-2.

Previous studies that examined the homeostasis of polyclonal T cells in PKB Tg overexpressing mice found an accumulation of CD4 T cells that were increased in size, albeit in a cytokine-sufficient environment [17]. Surprisingly, γc$^-$ M1 CD4$^+$ naïve T cells on a PKB Tg background alone or in combination with Bcl-2 over-expression still displayed a reduced cell size compared to γc$^+$ M1 CD4$^+$ naïve T cells, indicating that cellular metabolism was not restored [14]. Thus, although inhibitors of PKB can reduce the size of CD4$^+$ naïve T cells *in vitro* [12], it appears that a combination of signaling pathways is responsible for controlling cellular metabolism *in vivo*. Masse *et al.* [14] also observed that

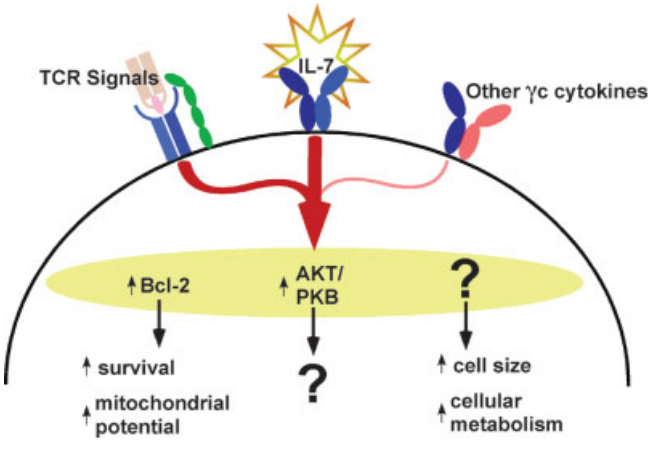

Figure 1. Multiple intracellular signals mediate the effects of IL-7 on the maintenance, metabolism and size of naïve CD4$^+$ T cells.

the number of $CD4^+$ naïve T cells is significantly reduced in γc^- mice in comparison to $CD127^-$ mice, indicating that γc cytokines other than IL-7 play a noticeable, but not essential role in the homeostasis of these cells [14]. The major conclusions of the current study are summarized in Figure 1.

Overall, an important step has been taken in regard to finding the precise signals that regulate the homeostasis of naïve $CD4^+$ T cells. Future studies will be needed to dissect the exact combination of signals stimulated by IL-7 that maintain the survival, size and metabolism of naïve $CD4^+$ T cells. Furthermore, it will be interesting to define the exact role of PKB. Understanding the mechanisms that specifically maintain naïve $CD4^+$ T cells could allow for their manipulation under conditions where they are known to diminish such as in the aged.

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