IMMUNOLOGY

Lymphocyte Survival: A Red Queen Hypothesis

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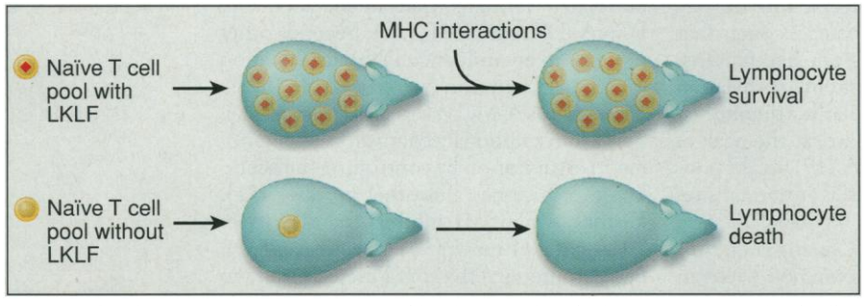
How can the immune system maintain its potential to respond to virtually all new foreign substances throughout life? This capacity requires the continuous presence of a pool of immune cells in the body— naïve T cells that express a vast array of T cell receptors, each responding to a different antigen. This diverse T cell repertoire is generated during T cell development in the thymus, which exports naïve resting mature T cells to other outposts of the immune system in the periphery. These naïve T cells were previously thought to have a rather dull existence, as they waited out their short life-span with no apparent functional activity (unless suddenly rescued by stimulation with foreign antigen to be activated for defense and then transformed into long-lived memory cells). The origin of naïve T cells in adults has also been unclear. As the thymus undergoes atrophy during puberty, how can the naïve T cell pool be maintained for the life of the organism?

On page 1986 of this issue, Kuo *et al.* (*1*) revise our view of the life of these cells and show that naïve T cell survival is an active process, probably dependent on the expression of particular sets of genes by resting T cells. They have identified a Kruppel-like zinc-finger transcription factor called lung Kruppel-like factor (LKLF) that is expressed in mature T cells but not in immature thymocytes. In contrast to most transcription factors that regulate new gene expression after T cell activation, LKLF is expressed only in resting cells and is down-regulated in vitro shortly after T cell activation. Kuo *et al.* studied the role of this transcription factor in lymphocyte development in RAG-2–deficient mouse chimeras in which all lymphocytes are derived from LKLF–/– embryonic stem cells. Without LKLF, these mice develop a normal B cell compartment and a normal-sized thymus, but the number of mature peripheral T cells is reduced by 90%. Moreover, all mature T cells with a naïve phenotype are absent in the thymus and the periphery. Therefore, naïve T cells lacking the LKLF transcription factor cannot survive (see the figure).



Running to stay in place. The presence of the transcription factor LKLF is essential for the survival of naïve T cells, the cells that respond to foreign antigens.

LKLF also seems to be required for another aspect of T cell survival. During immune responses, antigen-specific T cells are activated, divide extensively, become effector cells, and eventually dispose of the antigen. Most activated T lymphocytes are then believed to die by apoptosis and a minority to revert to a relatively more quiescent memory state. Effector and memory cells differ from naïve cells in surface markers and constitute about half of the peripheral T cell pool. (It is not yet clear how effector and memory cells may be differentiated from one another.) LKLF–/– mice lack 80% of this "antigen-experienced" T cell pool. This severe reduction of peripheral T cells is associated with high rates of apoptosis in vitro and in vivo; rates like those seen in T cells actively involved in ongoing immune responses. Therefore genes regulated by LKLF may also contribute to the survival of the relatively more quiescent memory cells.

The aphorism that naïve lymphocytes exist "waiting for the end" (*2*) is no longer true. Rather, naïve quiescent peripheral T cells are actively engaged in cell survival. Continuous major histocompatiblity complex (MHC) recognition is required for the persistence of these T cells: CD8 T cells require interactions with the MHC class I (*3*), and CD4 T cell survival is dependent on the presence of MHC class II molecules (*4*). It is not yet known whether this recognition is also required for LKLF expression. Memory cells, generated from naïve cells exposed to antigen, also require active signals for survival, but the signals are somewhat diffferent. While naïve CD8 T cells require the correct MHC class I restricting molecule to survive, memory CD8 T cells only require a nonspecific class I molecule. Moreover, lymphocytes in these two compartments each have autonomous homeostatic controls (*5*), ensuring the presence of naïve and memory cell pools. This organization allows the immune system to deal with pathogens that it encounters frequently and at the same time to keep a reservoir of diversity to face new unexpected antigenic challenges. How the repertoire of T cell specificities is modified by peripheral selection, the type of receptor interactions involved, the possible relations between these signals and the LKLF transcription factors, and the complex interplay of genes of the bcl-2 family in lymphocyte survival (*6*) have yet to be identified.

The comment by the Red Queen in *Through the Looking Glass*, "It takes all the running you can do to keep in the same place" (*7*) has been used to describe the role of active individual engagement in ensuring species survival and evolution (*8*). The new results by Kuo *et al.* (*1*) suggest that the peripheral immune system is running too (*9*).

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