IMMUNOLOGY

Selection for Survival?

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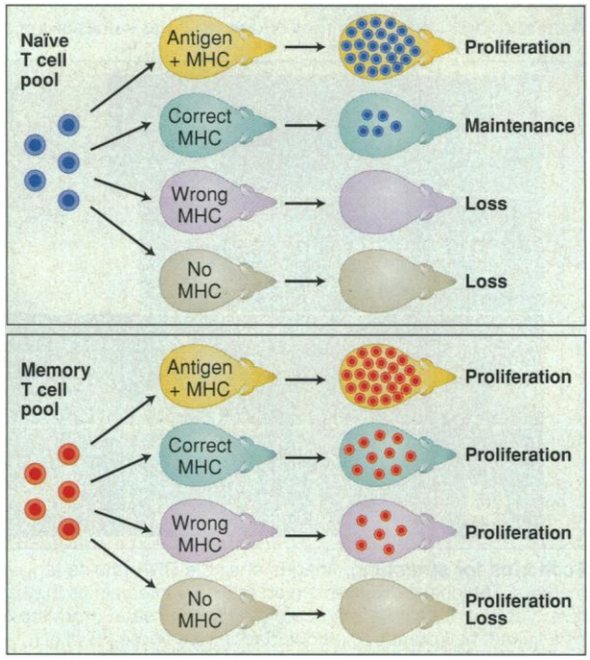
An organism's immune system must satisfy two contradictory requirements. On the one hand, it has to respond to a broad range of antigenic challenges from foreign substances. On the other hand, it should react to particular antigens quickly and efficiently, especially those pathogens that it encounters repeatedly. The immune system solves this dilemma by creating two compartments, one to meet each of these needs. The primary lymphoid organs (thymus and bone marrow) produce millions of lymphocytes displaying a vast diversity of antigen-specific receptors that form the basis of the broad immune response; these cells are exported to the peripheral organs (blood, spleen, and lymph nodes) where they form a "naïve" pool capable of recognizing most antigens. Upon antigenic stimulation, the relevant lymphocytes become activated, proliferate, and eventually dispense with the antigen. The second compartment is formed when some of the antigen-stimulated lymphocytes become diverted to a "memory" pool, composed of cells that can respond to antigen more immediately than those in the naïve pool. The memory cells differ from the naïve cells in their surface marker profiles, homing properties, signaling requirements, and cytokine secretion pattern (*1*).

What factors control the maintenance of these two pools, both of which are constantly subject to dynamic influences? The importance of this question is underscored by recent findings that HIV patients show perturbations in the homeostasis of lymphocyte populations (*2*). The difficulty in addressing this question arises from the labyrinthine complexity of the immune system. Now, by exploiting mouse strains engineered to have simplified immune systems, Tanchot *et al.* (*3*, page 2059) have begun to define the factors that drive the dynamics of the naïve and memory lymphocyte populations.

Tanchot *et al.* focus on the ligands required by the naïve and memory $CD8^+$ T cells for proliferation or survival in a mouse, clearly key control points for maintenance of the two pools. Classically, $CD8^+$ T cells become activated and proliferate when stimulated by a specific peptide antigen bound to a particular major histocompatibility complex (MHC) class I molecule expressed at the cell surface. Even in the absence of stimulation by specific antigen, naïve and at least some memory $CD8^+$ cells can survive for long periods in a normal mouse (*4*). Tanchot *et al.* used the strategy illustrated in the figure to define the precise ligand or ligands that allow the proliferation and long-term survival of these cells. To simplify the problem, they generated monoclonal $CD8^+$ T cell populations that expressed only one type of T cell receptor (TCR); the receptor is specific for the antigen HY (found only in males) presented by an MHC molecule called H-2D^b. The authors were sure these cells were all identical because they were derived from a transgenic mouse strain that could not rearrange its endogenous TCR genes. The naïve population was isolated directly from female mice engineered to express these uniform receptors on all of their $CD8^+$ T cells. The memory population was generated when some of the naïve cells were transferred into T cell–deficient mice that were male-female chimeras and so contained the stimulus for the naïve cells, HY antigen. The cells appropriately exhibited the patterns of surface marker expression and the cytokine secretion profiles expected of naïve and memory $CD8^+$ lymphocytes. To test what molecules these cells require for proliferation and survival, Tanchot *et al.* compared the cells' fate after their transfer into irradiated hosts that differed in their expression of the potential ligands. In addition to control animals containing the correct antigen (HY) and correct MHC class I molecules (D^b), cells were injected into animals without the antigen, animals with only an incorrect MHC class I molecule (K^b instead of D^b), or animals without any class I molecules at all.



Necessities of life. T lymphocytes that effect immune responses (naïve cells in blue) require continuous exposure to their correct MHC ligand for maintenance (and also antigen for proliferation), whereas memory cells that have previously responded to antigen (red) are less fussy and are maintained even in the presence of the wrong MHC ligand.

The naïve and memory $CD8^+$ T cell populations turned out to have quite different requirements for both proliferation and survival. As expected, both proliferated vigorously when they encountered the HY antigen and the correct MHC class I molecule, D^b. Yet memory, but not naïve, cells could also proliferate, although with reduced vigor, in the absence of antigen or of D^b, or even in the complete absence of class I molecules. Similar to previous reports (*4*), both the naïve and memory populations could survive for a prolonged period without intentional stimulation by HY antigen, but they did require some kind of "tickling" by MHC class I molecules or else they disappeared by 2 weeks after transfer. Naïve cells needed the correct class I molecule, D^b, whereas memory cells again seemed less particular, surviving in mice that did not express D^b but did display other (incorrect) class I molecules, although they disappeared rapidly in animals devoid of all class I molecules.

Because these results were obtained (of necessity) with a heavily engineered system, and, like findings with all such systems, might harbor unexpected artifacts, they need to be confirmed by independent strategies. This is important because the results of Tanchot *et al.* have several potentially interesting implications. First, the different requirements of naïve and memory cells for both proliferation and survival underline the

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distinctiveness of these two compartments. The memory $CD8^+$ population was clearly the less fastidious. Perhaps most striking was its ability to expand in the absence of specific antigen and to proliferate to a significant extent even in the absence of all MHC class I molecules. This observation recalls the recent finding that interferon-α can stimulate the proliferation of memory but not naïve $CD8^+$ cells in the absence of intentional antigenic stimulation (5). It is now imperative to determine how many such factors help to maintain the memory pool; in what contexts they are produced; how memory—but not naïve—cells stay attuned to them; and how they influence the mobilization of an antigen-specific memory response.

The fact that naïve $CD8^+$ T cells require contact with the correct MHC class I molecule in order to survive for prolonged periods in the periphery hints at a process akin to positive selection in the thymus. Positive selection favors export of a useful T cell repertoire by promoting the survival and differentiation of only those thymocytes that can productively interact with the MHC molecules expressed on thymic stromal cells. That such a peripheral selection process might be generally occurring is supported by two recent reports, relying on nontransgenic systems, that $CD4^+$ T cells survive for much longer periods in the periphery if they make contact with MHC class II molecules (6, 7). Some of the questions immediately raised are whether the repertoire of T cell specificities undergoes any significant further shaping as a result of peripheral selection, which peripheral cells need to express MHC molecules in order to enhance survival, and precisely what receptor interactions and internal signals are involved.

These new results preview a story that will demand our close attention as it unfolds.

References

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NEUROSCIENCE

Learning Mechanisms: The Case for CaM-KII

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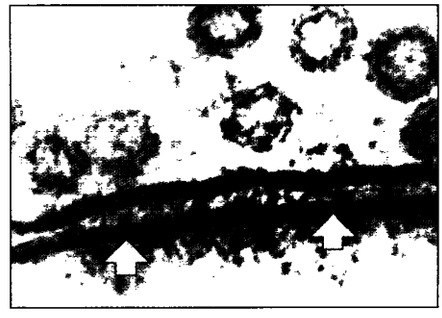
What are the long-lasting changes that occur in your brain as you learn new information? It is generally thought that memory is due to persistent modification of the strength of synapses, the structures that communicate information from one neuron to the next. One such modification is the long-term potentiation (LTP) that occurs at the synapses of the CA1 region of the hippocampus. This type of modification is of particular interest because it has associative properties that match that of learning itself (we come to associate the smell and taste of food), and because the hippocampus is important for long-term memory. The report by Barria *et al.* on page 2022 in this issue (*1*) is a significant step forward in our understanding of the persistent biochemical modifications that underlie this form of LTP.

The major new finding of Barria *et al.* is that the postsynaptic receptors (a subtype of glutamate receptor known as AMPA receptors) that mediate excitatory synaptic transmission at this synapse become phosphorylated after LTP induction and stay phosphorylated for at least 1 hour thereafter. The authors also show that phosphorylation of AMPA receptors in an expression system enhances the responses of these receptors to glutamate. Together with previous findings (*2*), these results provide strong evidence for a simple, postsynaptic mechanism for enhancing synaptic transmission during LTP.

The initial triggering event of LTP, believed to be a brief rise in postsynaptic calcium, results in the phosphorylation of AMPA receptors. What causes this modification and how is it maintained for at least an hour after the initial triggering event? A large body of evidence suggests that calmodulin-dependent protein kinase II (CaM-KII) is a critical player in LTP, and it has special properties that make it an attractive candidate for exhibiting persistent changes and serving as a memory molecule (3). CaM-KII is localized in the postsynaptic density, directly adjacent to the channels that mediate synaptic transmission (see the figure). The work of Barria *et al.* suggests that CaM-KII controls AMPA receptors directly, because the phosphorylation of AMPA receptors after LTP induction occurs at a site that can be phosphorylated by CaM-KII and is blocked by an inhibitor of CaM-KII. Theoretical (*4*) and experimental (5) studies suggest that the maintenance of the AMPA receptor phosphorylation may be due to the ability of CaM-KII to maintain its activity for long periods after its initial activation by calcium. The kinase may accomplish this by calcium-dependent autophosphorylation of the threonine residue at position 286, which renders its activity independent of calcium. This autocatalytic process could maintain the "on" state of the kinase for long periods, perhaps indefinitely. Indeed, Barria *et al.* provide support for this mechanism by showing that CaM-KII stays persistently phosphorylated at the 286 site for at least 1 hour after LTP induction [but see (6)]. Other kinases may also contribute to this persistent phosphorylation (7), as inhibitors of CaM-KII have failed to depress established LTP (8).

A simple and direct role for CaM-KII in triggering and perhaps maintaining LTP is supported by studies in which CaM-KII activity was acutely increased either with viral transfection (9), injection of the active enzyme (*10*), or injection of calcium and calmodulin (*11*). In these cases synaptic transmission is enhanced and LTP is occluded. However, recent work (*12*) with transgenic mice, in which constitutively ac-



Where LTP happens. The postsynaptic side of the synapse (arrows) is the site of persistent biochemical modifications that maintain LTP. [Photo courtesy of Kristen Harris]

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