Rebuilding the Thymus

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IMMUNOLOGY

Rebuilding the Thymus

Avinash Bhandoola[1] and David Artis[2]

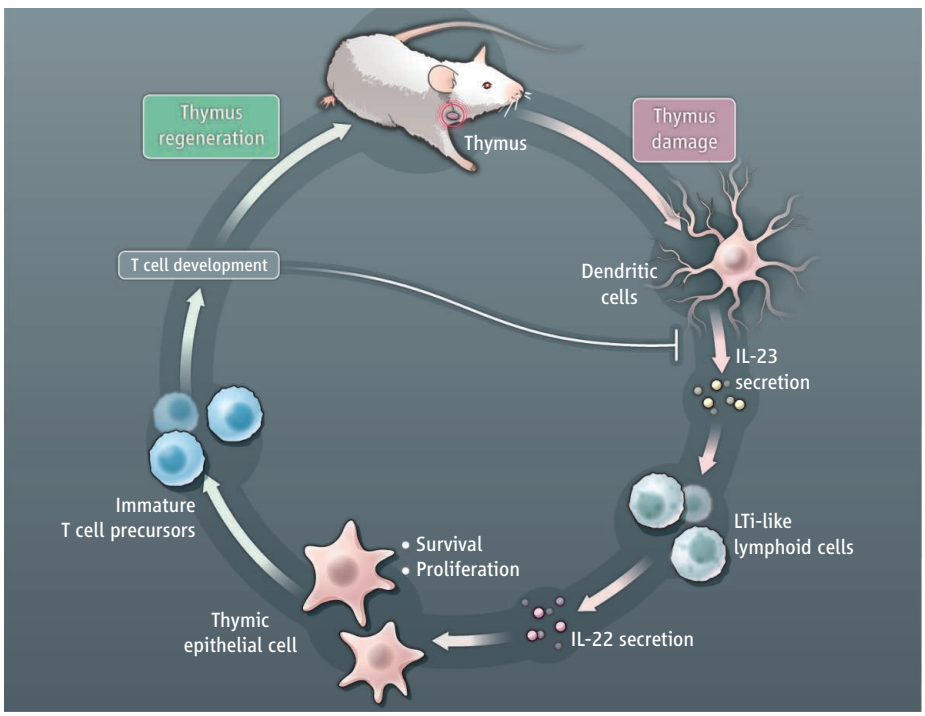
Innate lymphoid cells play a role in regenerating the thymus and restoring T cell development.

The thymus is the essential generative organ for T cell production, conserved from cartilaginous fish to humans (*1*). It is periodically colonized by lymphoid precursor cells from the blood, and after a period of maturation, T cells emerge bearing specific T cell receptors (*2*). This constitutes an arm of the adaptive immune system that provides many different modalities of protection. But many conditions affect thymus function, including therapeutic treatments such as chemotherapy and irradiation, with dire consequences for host protection (*3*). On page 91 of this issue, Dudakov *et al*. (*4*) demonstrate a surprising role for a subset of innate lymphoid cells in regenerating the thymus. This has implications for restoring and maintaining normal T cell immunity during conditions when thymus function is diminished.

The roles of innate lymphoid cells are poorly understood. Some populations have only recently been discovered (*5*) whereas other well-known immune cells, such as lymphoid tissue inducer (LTi) cells, are now considered part of this innate lymphoid family (*6*). LTi cells are required for initiating lymph node development in fetal mice, and they coordinate lymphoid tissue repair following viral infection (*7*, *8*). More recently, LTi-like cells have been shown to function outside lymphoid tissue development and maintenance in mice. After epithelial damage due to chemical or infectious stimuli, LTi-like cells respond to the cytokine interleukin-23 (IL-23) by producing IL-22 and IL-17 (*5*, *9*). These cytokines in turn direct the expression of antimicrobial proteins, and promote epithelial proliferation and tissue repair at barrier surfaces. Indeed, LTi-like cells appear to be the dominant source of IL-22 shortly after enteric bacterial infection in mice (*10*).

Dudakov *et al*. show that the cytokine circuit in which IL-23 activates LTi-like cells to make IL-22 also operates during thymic regeneration (see the figure). The authors discovered a population of lymphocytes within the mouse thymus identical to LTi cells on the basis of the expression of characteristic cell surface proteins (*5*). Furthermore, these intrathymic lymphocytes express the transcription factor RORγ(t), which is required for the development of LTi cells (*11*). To study the function of these intrathymic LTi-like cells, the authors depleted T cell precursors in the thymus by either total body irradiation or synthetic steroid administration in mice. Both conditions triggered production of IL-23 by intrathymic dendritic cells, which subsequently stimulated IL-22 production by intrathymic LTi-like cells. Further, thymic recovery was compromised in mice lacking IL-22 or IL-23. IL-22 may act by enhancing proliferation and survival of thymic epithelial cells, which are essential for T cell development. Administration of exogenous IL-22 accelerated thymic reconstitution after irradiation in mice, suggesting potential clinical utility. The results of Dudakov *et al*. are consistent with the known role for LTi-like cells and IL-22 in promoting tissue repair in the spleen, intestine, liver, and skin (*8*, *12*–*14*) and point toward a key role for intrathymic LTi-like cells in sensing thymic damage and acting locally to restore tissue homeostasis. In addition to chemotherapy and radiation insults, the thymus is adversely affected by various conditions (chronic stress, inflammation) and by processes such as thymic involution, which occurs with age and may explain the increased susceptibility to infection in the aged (*15*, *16*). The thymus also shrinks during pregnancy in response to reproductive steroid hormones. There is keen interest in learning how thymic function is normally controlled, as this is very poorly understood at present (*16*).

How do intrathymic dendritic cells and LTi-like cells sense the requirement for thymic and immune regeneration? Dudakov *et al*. examined different strains of mutant mice with engineered alterations in T cell development and found an inverse correlation between the number of immature thymic T cell precursors and the amounts of IL-22 and IL-23 produced in the thymus.



Cytokine circuit. Immature T cell precursors may normally inhibit production of IL-23 by thymic dendritic cells. If T cell precursors are depleted, dendritic cells may stimulate innate lymphoid cells (LTi-like cells), which stimulates proliferation and survival of thymic epithelial cells that support T cell development.

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However, the mechanisms by which thymic dendritic cells sense T cell precursor numbers have yet to be determined. One possibility is that T cell precursors produce factors that prevent IL-23 production by thymic dendritic cells. Loss of T cell precursors would therefore result in thymic dendritic cell activation and IL-23 production.

The role of LTi cells in thymic regeneration provides insight into an apparent puzzle—that innate lymphoid cell subsets possess functions that mirror those of helper T cells. Indeed, different innate lymphoid cells and helper T cell subsets produce combinations of a variety of cytokines (IL-17, IL-22, IL-5, IL-9, IL-13, interferon γ, and amphiregulin among others) (*5*). This suggests a close evolutionary relationship between the two cell types, but raises the question of whether unique and nonredundant functions even exist for innate lymphoid cells. Although both cell types may share effector functions, they are stimulated in different circumstances. Dudakov *et al*. indicate that intrathymic innate lymphoid cells are activated when generation of the T cell adaptive arm of the immune system is compromised. This reveals how innate and adaptive lymphocytes complement and regulate each other. For immunologists studying innate lymphoid cells, such surprises are likely to continue.

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APPLIED PHYSICS

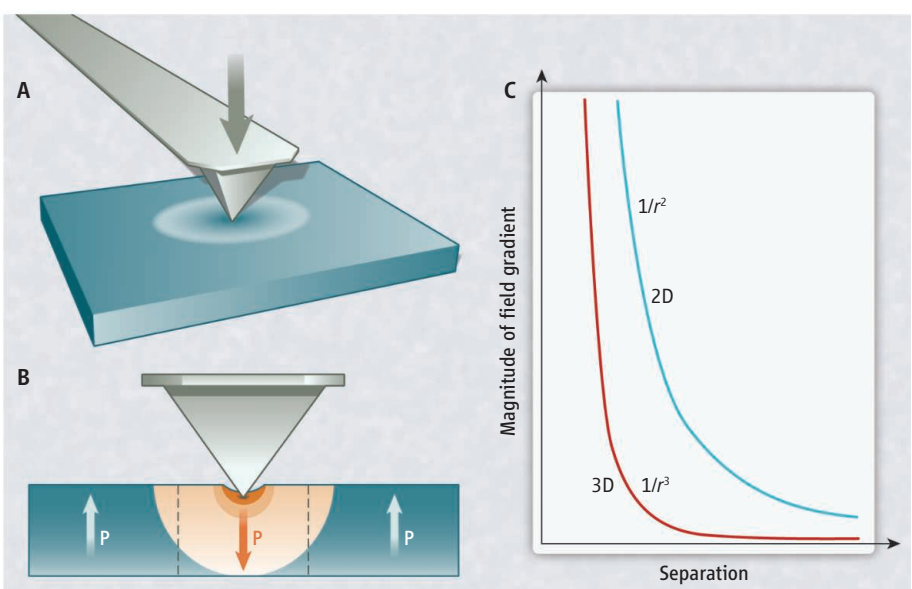
Stressing Ferroelectrics

Applying pressure with a scanning probe microscope tip causes the polarization state of a ferroelectric material to switch.

J. Marty Gregg

It is an obvious fact that falling objects accelerate due to Earth's gravitational field. It is much less obvious, however, that objects also stretch during free fall. The decay in the gravitational field strength with distance away from Earth's surface means that, during a fall, parts of objects closer to the ground experience a greater force of attraction than those farther away. This difference in attractive force between top and bottom produces a net stretching effect. It is not the field strength that causes stretching; rather, it is the change of field over distance, or field gradient, that matters. In extreme environments, such as those close to black holes, gravitational field gradients can be huge, causing such profound elongation that astrophysicists have coined a specific term, "spaghettification," to convey the change in shape suffered by objects in these exotic regions of space. In our everyday experience, however, effects resulting from field gradients are not usually strongly noticeable and are generally only considered to produce second-order effects of little consequence. Despite this, on page 59 of this issue, Lu *et al*. (*1*) have been able to cause a reversal in the direction of polarization in a ferroelectric material (ferroelectric switching) solely by using the induced gradient of an applied mechanical stress.

That uniform stress fields, without stress gradients, can alter electrical polarization is extremely well established and is called piezoelectricity. As a phenomenon, piezoelectricity became the focus of intense interest for naval research during the second World War. The primary reason was that piezoelectrics were found to both usefully generate and detect sonar pulses under water. One of the main figures in piezoelectric research during this time was L. E. Cross. Although not the first to suggest that stress gradients might also induce changes in electrical polarization (*2*–*5*), he was cer-



Under pressure. (**A**) Pushing the tip of the scanning probe microscope causes a stress gradient in the ferroelectric film that induces switching in the orientation of the local polarization (**B**). Field gradients are extremely short-range (**C**) and are therefore only likely to dominate overall material response in nanomaterials and ultrathin films where the entire system is close to the field source. Nanopatterning could extend the length scales for field gradient effects by reducing dimensionality: Compare the form of the $1/r^2$ and $1/r^3$ decay in field gradient with distance expected in 2D and 3D geometries, respectively.

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