PERSPECTIVES: IMMUNOLOGY

Exposing Thy Self

Pamela S. Ohashi

T lymphocytes of the immune system are crucial for generating a specific immune response against pathogens. However, a proportion of T cells recognize fragments of self proteins and must be eliminated during T cell development in the thymus by a process called clonal deletion. Self-reactive T cells that escape clonal deletion can cause autoimmune diseases such as multiple sclerosis and diabetes. On page 1395 of this issue, Anderson *et al.* (*1*) uncover a new way to promote the elimination of self-reactive T cells.

Immature T cells in the thymus express unique T cell receptors (TCRs) that are generated by random rearrangements of a variety of gene segments. These randomly generated TCRs are expressed on the surface of T cells and provide the diversity necessary to recognize the unforeseen world of foreign pathogens. During development in the thymus, the specificity of the TCR is tested, and any T cell carrying a TCR that efficiently binds to self molecules is eliminated through clonal deletion.

Although clonal deletion provides an effective way to purge the T cell repertoire of potentially harmful autoreactive cells, this process of inducing thymic tolerance is not absolute. One problem is that not all self proteins are expressed in the thymus, and so T cells carrying TCRs that recognize self molecules expressed by other tissues are not eliminated. To circumvent this problem, the immune system has developed ways to inactivate and eliminate self-reactive T cells outside of the thymus (peripheral tolerance). Indeed, other cells of the immune system, such as dendritic cells and regulatory cells, influence the activity of potentially autoreactive T cells (*2*–*4*).

In the thymus, there is plenty of evidence to show that "what you see is what you become tolerant to." Anderson and colleagues now add a new dimension to our understanding of thymic tolerance. They demonstrate that in mice, a transcription factor called autoimmune regulator or aire promotes the expression of a portfolio of tissue-specific self proteins by thymic epithelial cells that do not normally express these proteins. The thymic expression of these proteins permits the clonal elimination of tissue-specific T cells and thereby reduces the proportion of autoreactive T cells in the repertoire (see the figure).

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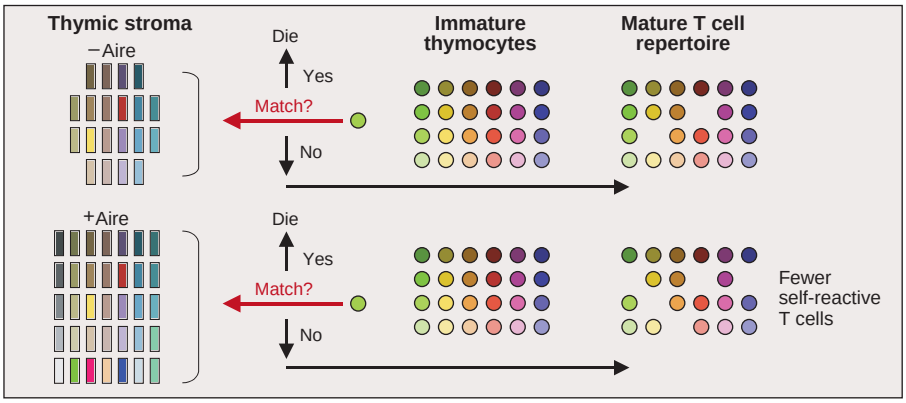
The *aire* gene, identified and characterized by two independent groups (*5, 6*), is expressed by epithelial cells in a region of the thymus called the medulla (*7, 8*). Interest in identifying the *aire* gene was sparked by a human autosomal recessive disorder called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED). This disease is characterized by autoimmune destruction of endocrine organs, the inability to eliminate *Candida* yeast infections, and growth of ectodermal dystrophic tissue. Researchers surmised that identification of the genetic mutation associated with APECED would give important insights into mechanisms of autoimmunity, because this is the only autoimmune disorder known to be inherited in a Mendelian fashion [reviewed in (*9*)]. Identification of the *aire* gene mutation in human APECED patients was followed by the generation of mice lacking this gene. Mice deficient in *aire* are susceptible to spontaneous autoimmune disorders similar to those manifested by APECED patients (*1, 8*). In addition to the production of tissue-specific autoantibodies, these animals show widespread inflammation of defined areas of a variety of organs, including the retina, ovary, testis, and pancreas.

The elegant study by Anderson *et al.* demonstrates the importance of aire for the expression of self proteins in thymic tissue and the promotion of thymic tolerance (*1*). Using bone marrow transplants to generate chimeric mice, the authors show that the defect underlying autoimmunity is associated with aire-deficient stromal cells which include the medullary epithelium of the thymus. Importantly, the investigators were able to transfer autoimmunity to naïve mice by transfusing them with lymphocyte populations from aire-deficient animals. These findings are consistent with the interpretation that the medullary thymic epithelial cells of aire-deficient animals cannot express aire and so cannot present tissue-specific self antigens to developing T cells. Accordingly, self-reactive lymphocytes are present in the mature T cell repertoire and provoke autoimmune disease when transferred to another recipient. Microarray analysis identified potential genes that are regulated by aire, many of which encode tissue-specific proteins such as insulin, thyroglobulin, and zona pellucida glycoprotein. Notably, the tissue-specific proteins identified by microarray analysis represent some of the aire target proteins recognized by specific autoantibodies from APECED patients.

The significance of the Anderson *et al.* study is twofold. It provides insights into the development of human autoimmune disease and the importance of thymic tolerance for preventing autoimmunity. Of particular importance is the role of the medullary epithelial cells in self tolerance (*10*). In addition, the new work suggests that evolution has selected for another layer of thymic tolerance regulation—that is, genes have evolved to ensure thymic expression of tissue-specific self antigens that are the target of autoimmune responses. Infertility has been reported in autoimmune patients and in mice carrying mutations in the *aire* gene (*1, 8, 9*). Aire promotes thymic expression of the zona pellucida glycoprotein, a known target self antigen in autoimmune ovarian disease (*1, 11*). Aire seems to provide protection against autoimmune destruction of the reproductive organs and may



Aire and autoimmunity. Aire regulates autoimmunity by promoting expression of tissue-specific proteins in the thymus. Thymic stromal cells in both the cortical and medullary epithelium collectively express a variety of self molecules (different colored squares). Immature thymocytes express defined T cell receptors (TCRs), each with a unique specificity depicted by a different colored circle. Each thymocyte is tested for its ability to recognize a self protein. If the specificity of the TCR matches a self protein (same color), then the T cell is deleted from the repertoire. Aire promotes expression of a greater number of different self proteins in the thymus, particularly tissue-specific proteins. The chances of autoimmunity are thus decreased because a greater number of self-reactive T cells are eliminated in the thymus through clonal deletion.

have been strongly selected for because of its importance for maintaining fertility.

It is clear that expression of tissue-specific self antigens in the thymus is sufficient to prevent autoimmunity (*12, 13*). The straightforward mechanism that would explain why aire-deficient mice develop disease is that pathogenic self-reactive T cells were not eliminated by clonal deletion. However, further studies are needed to understand how tissue-specific T cells escaped tolerance induction in the periphery, and to identify the events that trigger autoimmunity in the aire-deficient mice. Another explanation concerns immune regulatory cells that may be generated by self proteins in the thymus (*14*). The absence of these regulatory cells in aire-deficient mice or humans would provide an environment that encourages the development of autoimmunity (*15*). Although further studies are needed, current evidence suggests that the aire-deficient mice develop an autoimmune profile similar to that of mice depleted of regulatory cells [reviewed in (*11*)]. Further exploration of mice that lack aire will provide exciting insights into the mechanisms and initiating events of human autoimmune disease.

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PERSPECTIVES: COSMOLOGY

A New Window to the Early Universe

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The big news at the recent Cosmo '02 workshop in Chicago (*1*) was the announcement of the first detection of polarization in the cosmic microwave background (CMB), the 2.726 K radiation left over from the big bang (*2*).

In 1968, Rees predicted that the CMB must be polarized if it is a relic from the early universe (*3*). Ever since, astronomers have sought observational evidence. The race for detection heated up after precise measurements of temperature fluctuations (*4–8*) provided increasing confidence in our ability to understand the CMB. The new discovery, reported by the Degree Angular Scale Interferometer (DASI) collaboration, not only confirms our theoretical grasp of the CMB, but also opens a whole new window to the early universe.

Early-universe cosmology merges the search for new laws of fundamental physics, beyond the standard model of particle physics and Einstein's gravity, with the search to understand the origin and evolution of the universe. The mean thermal energies of the particles that filled the universe microseconds after the big bang greatly exceed those accessible with the most powerful terrestrial particle accelerators. The early universe thus provides a test bed for new ideas in ultrahigh-energy physics—if it has left a trace in today's universe, the big bang's cosmic debris. Fortunately, a truly pristine cosmological relic exists: the CMB.

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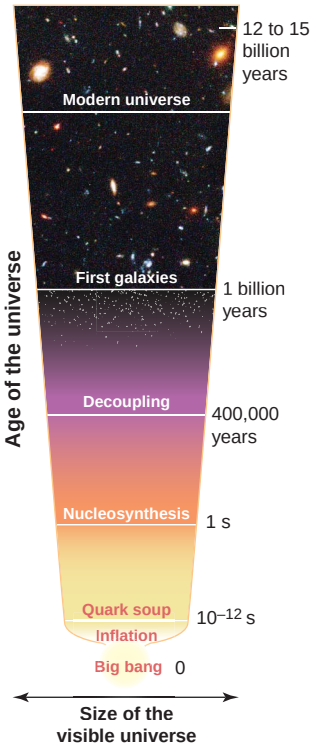
To a good approximation, the temperature of the CMB radiation is the same in all directions in the sky. However, at the level of 1 part in 10^5, there are small variations. The CMB radiation was emitted ~14 billion years ago when electrons and nuclei first combined to form atoms, at a time when the universe was ~400,000 years old. Thus, the angular temperature variations reflect variations in the properties (such as density, pressure, temperature, and velocity) of the primordial universe.

The temperature patterns at the CMB surface of last scatter were probably inscribed even earlier, just fractions of a microsecond after the big bang. Particle theories suggest that in the extreme temperatures that existed then, gravity may have briefly become a repulsive, rather than attractive, force. The enormously accelerated expansion during the ensuing period of "inflation" can explain the remarkable smoothness of the CMB and produce the primordial mass inhomogeneities imprinted in the CMB temperature.

Existing CMB temperature maps allow the temperature power spectrum, which quantifies the size distribution of hot and cold spots, to be determined. Comparison with predictions of inflation models for primordial inhomogeneities then provides constraints for several cosmological parameters (such as the mass density, the geometry of the universe, and its expansion rate). Moreover, the oscillatory pattern seen in the CMB power spectrum (*9*, *10*) confirms that the primordial inhomogeneities are consistent with inflation.

The CMB polarization contains yet more cosmological data than that provided by the temperature maps alone. Most light is unpolarized (the orientation of the oscillating electric field that makes up the electromagnetic wave is random). But light can also be linearly polarized (the field is more likely to oscillate in a given direction). In the CMB, the polarization indicates a direction at the surface of last scatter. However, the polarization amplitude is very small—just ~7% of the temperature-fluctuation amplitude for the polarization from primordial inhomogeneities.

Inflationary models make many predictions for the statistical properties of the polarization (*11*).



From smooth to structured. The big bang may have been followed by a period of rapid inflation, during which the resulting "soup" of particles coalesced into nucleons and lighter elements. Matter and radiation eventually became decoupled, the former gravitationally clumping into the structure of the modern universe and the latter yielding the microwave background we see today. The seeds from which galaxies grew should be apparent in the variations in the radiation background.