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Recognizing Self from Nonself

Of all the mysteries of modern science, the mechanism of self versus nonself recognition in the immune system ranks at or near the top. The immune system is designed to recognize foreign invaders. To do so it generates on the order of 10^{11} different kinds of immunological receptors so that no matter what the shape or form of the foreign invader there will be some complementary receptor to recognize it and effect its elimination. The ability to respond to any foreign substance no matter how contemporary or how bizarre is puzzle enough, but the added mystery is that the immune system can distinguish foreign carbohydrates, nucleic acids, and proteins from those that exist within the organism, often in shapes barely distinguishable from the invaders. When the immune system is working well it never gets activated by self substances, but unerringly responds to the nonself substances. When the system is not working well this distinction gets blurred and diseases of autoimmunity occur.

As might be expected from the importance and the difficulty of the task that it must perform, the immune system is extremely complex. These cells can unleash powerful binding and enzymatic forces that must contain and expel toxic substances ranging from molecules to whole cells, and yet not allow these forces to damage the delicate machinery of the body.

The mechanism by which this self-nonself distinction is achieved is beginning to be understood. The cells of the immune system (the B and T lymphocytes) are rendered tolerant to their own organism's molecules by two processes, one that results in elimination of the cell that would otherwise produce an anti-self response (clonal deletion), and another that results in their inactivation (clonal anergy). The combination of papers in this special issue, assembled under the editorial supervision of Linda J. Miller, addresses the steps that have led to that conclusion and the new research to delineate the process in molecular terms. Each of these investigators uses a different system and a different approach to the problem. Blackman, Kappler, and Marrack, for example, examine the paradox that T cells that bear these receptors can be either stimulated to proliferate (positive selection) because they have some degree of complementarity, or become inactivated (negative selection) because their affinity to self MHC (major histocompatibility complex) or self peptide is so high that the clones are deleterious. Ramsdell and Fowlkes use chimeric mice to clarify the role of the thymus in the inactivation of developing T cells. Schwartz, on the other hand, uses an in vitro model of tolerance to show that clonal anergy makes a T cell incapable of producing its own growth hormone, interleukin-2. Sprent, Gao, and Webb use chimeric mice to compare tolerance induction in developing versus mature T cells, since one theory suggests that deletion occurs in young cells, whereas anergy primarily occurs in more mature cells. Burkly, Lo, and Flavell use transgenic mice to examine the role of MHC molecules that are expressed outside of the thymus in inducing tolerance. Von Boehmer and Kisielow also use transgenic mice, but they examine the events within the thymus that affect T cell development and show that the binding of the T cell receptor to MHC molecules directs differentiation (positive selection). Goodnow, Adelstein, and Basten use transgenic mice to study tolerance in B cells and find that both deletion and inactivation occur. Sinha, Lopez, and McDevitt focus on those systems in which the discrimination breaks down and diseases of autoimmunity occur. About 5 to 7 percent of the population are subject to autoimmune diseases, which include insulin-dependent diabetes mellitus, multiple sclerosis, rheumatoid arthritis, myasthenia gravis, and psoriasis. Van Rood and Claas examine the complex process of the immune system in its responses to transplantation of organs from one human being to another. The goal is to generate lifelong tolerance to a foreign organ in mature adults, just as can be induced in a newborn mouse.

The general framework that arises suggests that during maturation the lymphocytes first rearrange the genes needed to make receptors specific. If at this immature stage a cell is exposed to an antigen or the peptide-MHC complex, it is either killed or becomes inactivated. Only the cells that respond to nonself should survive to maturity. Although recent work on tolerance has emphasized T cells, which have different functions than B cells, new studies suggest that both follow similar patterns in self-nonself activation and suppression. The understanding at the molecular level will not only be a solution to a fascinating intellectual puzzle, but offers practical suggestions for treating very serious diseases.—DANIEL E. KOSHLAND, JR.