Editorial & Letters

EDITORIAL

Halting the March of the Immune Defenses

The cells of the immune system stand as sentries at our epithelial borders and are deployed in our peripheral lymphoid tissues to defend against the constant onslaught of microbial invaders. The components of the innate immune system use a limited repertoire of receptors to recognize molecular patterns common to pathogens and provide us with an early warning system to identify and ward off unfriendly challenges. But many pathogens have evolved tricks to sneak through and disarm these innate defensive barriers.

Thus, it is up to the adaptive immune system, consisting of T and B lymphocytes, to provide us with our ultimate defense against many pathogens and with a memory of these encounters when rechallenged by the same pathogen. The system is adaptive because it has a dynamic repertoire of antigen receptors. The repertoire changes with each encounter with a pathogen, with the goal being ever more efficient eradication. How mammals can develop and maintain such a lethal defense system without ultimately harming themselves is a question being actively pursued by many investigators. How does the system get stunted by developmental mutations? How are autoimmune attacks avoided? How is an immune response that has done its job removed from the front line? How are the inherent weaknesses of immune defenses exploited by pathogens? Some of the answers are revealed in three Articles presented in this issue of *Science*.

T and B lymphocytes develop, mature, and learn the difference between self and nonself in the thymus and bone marrow, respectively. Their antigen-specific receptors serve as highly specific sensors to detect pathogens. The receptor assembly process is rigorously tested at quality control checkpoints. Cells without receptors or with inappropriately autoreactive receptors are discarded. In the Article by Fischer and Malissen (p. 237), the critical importance of the events involved in the assembly of and signaling by antigen receptors at each of these developmental checkpoints is revealed by the human or murine immunodeficiencies that result from mutations in components of the assembly process, signaling apparatus, or response machinery. The lessons learned from studies of these human and murine immunodeficiencies are excellent examples of how study of clinical diseases and basic biology can synergize in the discovery process.

The immune system has powerful weapons to unleash against pathogens, consisting of antibodies, cytokines, and cytolytic activities. However, excessive or unrestricted use of this arsenal can result in injury to the host, as can occur in autoimmune diseases, or in the excessive response to some bacterial toxins, such as toxic shock syndrome and food poisoning. Thus, it is critical that an immune response be measured and self-limited. Insights into the regulatory constraints placed on B and T cell responses are summarized by Van Parijs and Abbas (p. 243). These regulatory mechanisms determine the basal state of the immune system and help to limit the magnitude and duration of the adaptive immune response. It is interesting, as the authors note, that these key regulatory mechanisms do not appear to be redundant. Without backups, the failure of these regulatory mechanisms results in an immunologic army that is out of control.

Unfortunately, every army has its weaknesses, and microorganisms have developed a variety of strategies to exploit those of the immune system. The current pandemic of the human immunodeficiency virus is a consequence of its direct attack on one of the critical components of the immunologic armamentarium, the $CD4^+$ T cell. Ploegh describes some of the other elegant strategies adopted by pathogens to evade the immune system (p. 248). Some organisms have targeted intracellular antigen processing and presentation. This compromises the ability of the host to display antigenic peptides by interrupting the peptide antigen presentation by class I or class II major histocompatibility complex molecules on the cell surface. Thus, the immunologic army that cannot see the enemy cannot fight the enemy. Other pathogens have acquired variant cytokines, receptors, regulators of transcriptional responses, or inhibitors of apoptosis to evade, confuse, or inhibit the immune defense system.

Continued study of how the immune system can be tripped up, either through mutation or by deliberate assault, can potentially provide therapies to ensure that our immune defenses cannot just match, but beat, the world's pathogens at their own game.

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LETTERS

Connections

Readers describe what can happen when scientists cross national borders for collaboration and education (right, Red Sea Program participants). Researchers discuss the microscopic anatomy of "regenerating axons." And could the Internet suffer a "tragedy of the commons"?

Mideast Peace and Scientific Collaboration

The News & Comment article "As Mideast peace process lags, science endures" by Jocelyn Kaiser (6 Mar., p. 1447) illustrates a human aspect of science often neglected in the media. I would like to offer an example of such collaborations with the potential to help heal enmities between two peoples.

A number of Jewish scientists have participated in a collaboration between U.S. universities and Saudi Arabia. While on the faculty at Yale University School of Medicine, during discussions with Saudi and Yale collaborators, I wrote a computer application designed to help improve the care (and our understanding) of several severe pediatric illnesses in Saudi Arabia. I also spent some weeks as a guest of the sponsoring institution, King Faisal Specialist Hospital and Research Centre, living in downtown Riyadh and working with Saudi scientists and physicians. Others Jewish scientists at Yale and several other U.S. universities were similarly involved in clinical care and medical research collaborations. I enjoyed much hospitality and learned a lot from the intercultural discussions with my hosts.

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Southeast Asian Scientists and U.S. Graduate Programs

I enjoyed reading the article "Scientific growth faces fiscal crisis" by Jeffrey Mervis and Dennis Normile (Science in Southeast Asia, 6 Mar., p. 1466). One of the primary reasons that only sporadic attention is given by Americans to research efforts in Southeast