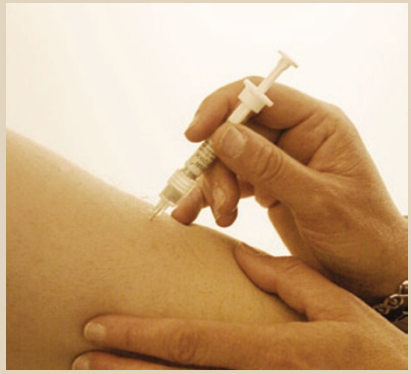
Rechallenging immunological memory


James King-Holmes / Photo Researchers, Inc.

The adaptive and innate arms of the immune system coordinate to respond to a secondary infection, resulting in both antigen-specific bactericidal activities and 'bystander' killing of unrelated pathogens, according to a recent report in *The Journal of Experimental Medicine* (**204**, 2075–2087).

After a foreign pathogen is encountered in an initial infection or vaccination, long-lived immunological memory is believed to be primarily in the hands of memory T cells. Once re-exposed to that pathogen, the armed memory $CD8^+$ T cells quickly mount their killing campaign against infected cells. In an antigen-specific process, they release interferon (IFN)-γ and tumor necrosis factor (TNF)-α to control the growth and clearance of the pathogen. $CD8^+$ T cells were thought to manage this process independently.

Emilie Narni-Mancinelli *et al.* have challenged this concept by demonstrating that the response to secondary infection is not solely dependent on memory T cells. Instead, activation of innate mononuclear phagocytic cells (MPCs) by the memory T cells is the necessary step for the final elimination of bacteria.

Upon re-exposure to the pathogen, existing memory T cells released the chemokine CCL3 to activate MPCs. MPCs released TNF-α, which in turn caused neutrophils and other MPCs to produce radical oxygen intermediates (ROIs) to clear the bacteria. The memory T cells by themselves were not sufficient to clear the infection, and blocking CCL3, TNF-α or ROIs prevented bacterial clearance.

Interestingly, an unrelated pathogen that is sensitive to ROIs was also cleared following the activation of innate cells during the secondary infection. When mice were immunized with bacteria and infected with another ROI-sensitive parasite, the mice cleared the remaining bystander parasite effectively during the secondary bacterial infection.

These findings have a number of clinical applications. For instance, in the past, measurements of TNF-α and IFN-γ have been used to determine vaccine efficacy. This work suggests that CCL3, the crucial link for MPC activation and ROI production, could be a superior readout, because it better represents the activity of memory T cells. This knowledge could also change the way we think about vaccinations. Memory responses could be manipulated to eliminate microbes that have developed resistance to multiple drugs, such as *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Perhaps the triggering of memory T cells specific to a previously received, unrelated pathogen could be used to activate ROI-producing MPCs to clear these or other new infections.

—Kate Jeffrey

Not so fast: adaptive suppression of innate immunity

Noah W Palm & Ruslan Medzhitov

The innate and adaptive immune systems act in concert to effectively combat infection while minimizing collateral damage caused by the host immune response. T cells of the adaptive immune system have now been shown to suppress overzealous early innate responses to infection that can lead to 'cytokine storm'–mediated death (pages 1248–1252).

Morbidity and mortality from infectious diseases can be caused either by direct damage to the host by the pathogen or by collateral damage to host tissues by the immune response to the pathogen. This collateral damage is referred to broadly as immunopathology and can result from overproduction of inflammatory signals by immune cells.

Mammalian hosts employ two interconnected systems—innate and adaptive immunity—to protect themselves from infection while minimizing immunopathology. We are only beginning to understand how these two systems are coordinated to maintain this delicate balance. It is generally thought that innate immunity combats infection immediately, whereas adaptive immunity reacts only after a delay of several days. This suggests that adaptive immunity should not influence the early innate response. In this issue of *Nature Medicine*, however, Kim *et al.*[1] reveal that T cells of the adaptive immune system actively suppress the cells of the innate immune system to prevent an overzealous early innate response and severe immunopathology.

Unlike invertebrates, which rely exclusively on innate immunity, mammals require both innate and adaptive immunity for an effective host response to infection. As the first line of defense, the innate immune system senses infection through pattern-recognition receptors, which recognize conserved molecular features of pathogens that are unique to microbial life forms[2]. These pattern-recognition receptors, such as the Toll-like receptors (TLRs), trigger a variety of antimicrobial responses to combat the infection. When the innate immune system is unable to contain an infection, the cells of the adaptive immune system step in as a second line of defense.

T and B lymphocytes of the adaptive immune system use randomly generated antigen receptors and, once activated, maintain a long-term memory of previously encountered pathogens[3]. These lymphocytes, however, cannot reliably distinguish 'self' from 'non-self', and so they rely on the innate immune system for instructions on when and how to respond to infection[2]. In turn, activated T and B cells further activate and direct innate defenses: T helper 1 (Th1)

Noah W. Palm and Ruslan Medzhitov are in the Howard Hughes Medical Institute and the Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06405, USA.
e-mail: noah.palm@yale.edu or ruslan.medzhitov@yale.edu