

JANUARY 26, 2009

Total Recall: Immune System Has a New Type of Memory

Howard Hughes Medical Institute (HHMI) researchers have discovered a new form of cellular memory that appears to help immune cells “learn” from past encounters with pathogens so they can combat them more effectively the second time around.

The new experiments show that natural killer cells – the rapid-response sentinels that destroy cells harboring viruses and other pathogens – have a previously unrecognized ability to recall their previous call to duty. HHMI researcher Wayne M. Yokoyama and his colleagues at Washington University School of Medicine report their findings in the January 26, 2009, issue of the *Proceedings of the National Academy of Sciences*.

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— **Wayne M. Yokoyama**

“Although the concept of immune system memory is not a new idea, it has generally been thought of as only a component of the adaptive immune system,” said Yokoyama. He said that the adaptive immune system, which is slower to initially respond to invaders, is especially effective in a second infection because it remembers previous battles with specific pathogens. The new findings add to growing evidence from Yokoyama’s lab and others that the innate immune system has previously unrecognized layers of complexity. Innate immunity, he says, is much more than “a primitive response blindly firing during infection.”

The protective cells that comprise the mammalian immune system fall into two broad and complementary arms. The body's first response to infection rallies elements of the innate immune system, which responds to infection uniformly and with limited specificity, said Yokoyama. This early response is bolstered by the adaptive immune system, which kicks in later. “This arm of the immune system has an amazing capacity to file away and recall the specific molecular features of any pathogen it has encountered in the past and responds more robustly the second time around,” said Yokoyama.

Yokoyama suspected natural killer cells might also have memory of their own. To put that idea to the test, Megan Cooper in his group isolated natural killer cells from mice, and then exposed those cells in culture to cytokines. Cytokines are hormone-like proteins that help activate immune system cells during infections. After they bathed the natural killer cells in cytokines overnight, the scientists injected those cells back into their mice.

“The mouse is like an incubator and we could detect the (previously activated) cells 10 to 21 days later,” Yokoyama explained. The team then reexposed the immune cells to cytokines, and monitored how both the previously activated cells and the mouse's resident population of unaltered natural killer cells responded.

“What we could show is that if cells were previously activated, they were much better at responding the second time around,” Yokoyama said. “We're not claiming antigen specificity. We're saying after the cell responds once, the next time around it responds better. We've discovered an aspect of memory independent from antigen specificity.”

According to Yokoyama, the experiments also showed that the capacity to remember past exposure to cytokines is heritable. When an activated natural killer cell divides, its memory is passed along to its daughter cells. “It appears to be a property that is intrinsic in the cell itself,” he noted.

Yokoyama speculates that these memory features could be boosted to fight infections and may exist in other parts of the innate immune system. His group is now planning studies to see if they can uncover evidence to support these ideas.