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Learning How a Virus Evades the First Line of Immune Defense

Researchers have uncovered the first evidence that a virus can mutate to evade the body's first line of immune defense. The discovery may help explain why people with AIDS or others with compromised immunity may suffer severe infections from viruses that they would otherwise defeat.

In studies published in the June 2004 issue of the journal *Immunity*, the researchers found that the mouse version of cytomegalovirus (MCMV) is capable of mutating to evade natural killer (NK) cells. NK cells are major weapons of the innate immune system, the component of the immune system that attacks infections first. This more generalized component of the immune system quickly springs into action to knock down infections. In the process, it buys precious time for the immune system's more specific second line of defense, known as acquired immunity, which must adapt and proliferate to target a particular invading virus or microorganism.

Howard Hughes Medical Institute investigator [Wayne M. Yokoyama](#) at Washington University School of Medicine in St. Louis led the research group. Yokoyama and his colleagues collaborated with researchers from the Max von Pettenkoffer-Institute in Germany and the University of Rijeka in Croatia.

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Although it has long been known that viruses such as HIV can mutate to evade the immune system, those mutations permit the virus to circumvent acquired immunity, said Yokoyama. Previous studies suggested that only RNA viruses underwent mutation and escaped, rather than the DNA viruses, whose replication is believed to be less prone to rapid mutation.

In earlier studies with mice, Yokoyama and his colleagues had shown how MCMV triggers NK cells to attack and kill cells infected with the virus. They demonstrated that the virus makes a protein called m157. The presence of this viral protein on the surface of an infected cell allows NK cells to recognize and destroy it.

In the experiments described in the *Immunity* article, the researchers exposed mice lacking an acquired immune system—but with normal NK cells—to MCMV. They discovered that although the mice survived initially, they died within several weeks of infection.

“That was a surprising finding, and it raised many questions about what the virus was doing during this period,” said Yokoyama. “Our subsequent analysis revealed that the viruses that grew out at three to four weeks after infection were not the same genetically as the ones that we put in.” The researchers found that the MCMV virus that eventually overcame the innate immunity of the mice had developed mutations in the gene for m157 that rendered the virus essentially “invisible” to NK cells.

One question, however, was whether the mutant m157 pre-existed in a small percentage of the viruses in the initial infection or whether the virus produced new mutations as it replicated, said Yokoyama. To show that the virus could, indeed, produce new mutations, the researchers infected mice with a viral culture that they knew contained no mutant m157. They found that there were different m157 mutations in each mouse, suggesting that mutations were independently developing in each infected mouse, allowing the viruses to escape detection by NK cells.

“These findings strongly support the idea that there are mutations that occur in the course of a single infection and these mutants escape immune control as a result of selection pressure,” said Yokoyama. “We believe this is a new concept because, although such viral escape has been described before, it has been in RNA viruses, which have a high propensity for mutation. Whereas, for double-stranded DNA viruses such as CMV, it has been thought that the mutation frequency was much lower.

“The other important aspect of this work is that, to my knowledge, this is the first example of a virus mutating to escape innate immunity,” said Yokoyama.

According to Yokoyama, the new findings may help explain why people with damaged acquired immunity—such as those with AIDS, autoimmune diseases or transplant recipients who are on immune-suppressing drugs—often suffer severe CMV infections.

“For example, AIDS patients with significantly depressed CD4 T-cell counts often get severe CMV infections, even though most people have had CMV infections that do not cause such severe disease,” said Yokoyama. “As a

physician, I've taken care of many of these patients, and it never dawned on me that there was something different about their virus that could produce such infections." Yokoyama also noted that transplant patients frequently develop CMV infections that may be due to presence of the virus in the transplanted organ. He said the infections tend to occur about a month after the transplant.

Given this clinical experience, Yokoyama and his colleagues now seek to extrapolate their findings to human CMV to determine whether the virus is undergoing the same type of mutation to evade the innate immune system. Such findings in humans, he said, could lead to new treatment strategies to combat viral infections.