Herpes infection may be symbiotic, help beat back some bacteria

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Mice with chronic herpes virus infections can better resist the bacterium that causes plague and a bacterium that causes one kind of food poisoning, researchers report in this week's *Nature*.

Scientists at Washington University School of Medicine in St. Louis attributed the surprising finding to changes in the immune system triggered by the long-term presence of a latent herpes virus infection. In latent viral infections, the virus is present for the lifetime of the host in a relatively quiescent form that does not cause overt symptoms.

While presenting their results, researchers stressed that they did not want to minimize or in any way disregard the human suffering and health risks caused by disease-causing herpes infections. But they noted that several strains of herpes viruses found in much of the human population remain symptom-free throughout the host's lifetime.

"Our results suggest that we should look at whether humans receive similar advantages from these and other chronic infections that do not cause active disease," says senior author Herbert W. "Skip" Virgin, M.D., Ph.D., head of the Department of Pathology and Immunology. "If so, that has public health implications because we would want to very carefully weigh the risks and benefits of eliminating a virus that our bodies have established a symbiotic relationship with."

Scientists previously used vaccination to eliminate the deadly and highly contagious smallpox virus. Vaccines are currently in use or in clinical

trials for several disease-causing strains of herpes.

Human herpes viruses include oral and genital herpes, the chickenpox virus, cytomegalovirus, Epstein-Barr virus and Kaposi's sarcoma-associated herpes virus. During an initial period of acute infection, many of these viruses cause symptoms, such as fever, cold sores or blisters. They then enter periods of latency. Sometimes symptoms never recur; sometimes they flare up periodically before becoming quiescent again. In addition, less infamous herpes viruses like HHV6 and HHV7 permanently infect most humans without ever producing any significant symptoms.

The results have potentially wide-reaching implications for immune research. Humans and other mammals have spent millions of years living and evolving with latent viral infections, Virgin notes, and the new results imply that infections may have altered our immune systems at a fundamental level. This could mean the virus-free animal models scientists use to study vaccines, autoimmune diseases, and other immune system issues have the potential to produce misleading results.

"Chronic virus infections may in part define what a normal human immune response is," says Virgin, who is the Edward Mallinckrodt Professor of Pathology and Immunology. "We may need to think about that as we consider the implications animal model results hold for human diseases."

Scientists have recognized for years that many types of bacteria and other microorganisms live in the human gut to the advantage of both the microbes and their human hosts. The results from the Virgin lab are among the first to suggest the potential for symbiotic benefits from viral infections that live in areas beyond epithelial surfaces like the skin, throat or intestines.

For the new research, Virgin's group worked with strains of mouse herpes virus closely related to human Epstein-Barr virus, Kaposi's sarcoma-associated herpes virus and cytomegalovirus. During studies of how mouse herpes viruses transition from acute to latent infections, Virgin made a discovery that piqued his interest in the possibility that latent infections might confer unrecognized benefits.

"We found evidence that the mouse immune system controls latent herpes infections in part by increasing production of a protein hormone called interferon gamma," Virgin says. "This is a signaling hormone that in effect puts some immune system soldiers on yellow alert, causing them to patrol for invaders with their eyes wide open and defense weapons ready."

Other scientists previously had shown that interferon gamma helps the immune system fight off some strains of bacteria. This led Virgin and his colleagues to test herpes-infected mice with exposure to the bacteria Yersinia pestis, which causes plague, and Listeria monocytogenes, which is a minor cause of food poisoning and can infect the central nervous system. Many aspects of Listeria infection in mice are also similar to those that occur in humans infected with tuberculsis. They found that when mice had a latent herpes infection, the bacteria replicated more slowly and were less likely to kill the mice.

When herpes was still in the acute phase of infection, no protective effect was present. When scientists exposed the mice to a mutant herpes virus that can infect but cannot establish latency, the herpes infection did not confer resistance. The protective effect could be produced by two different mouse herpes viruses.

"We have a good feel for who the main players are in this protective effect, but we need further research to better understand the exact mechanisms that underlie the process," Virgin says.

He suspects that the virus may be prompting the immune system to produce more interferon gamma to keep itself from emerging from latency. If the virus stays latent, it prevents itself from seriously endangering the host and can continue to spread to new hosts from its current perch.

"We need to explore whether there are additional costs and benefits to the host from this," Virgin says. "Are there additional pathogens that find it harder to come in as a secondary infection after herpes becomes latent" Do other latent infections convey similar protective effects" These are not the kinds of questions we're accustomed to asking about such infections, but our findings suggest that we need to start."

Virgin notes that human and mouse herpes viruses are genetically very closely related. The similarity strongly suggests that modern herpes viruses are likely descended from herpes viruses that infected evolutionary ancestors common to both mice and humans.

"That means that for as long as we've been human, these viruses have been with us," he says. "In that respect—given the millions and millions of years that mammalian immune systems have had to adapt to these viruses—perhaps these results are not as surprising as they might seem at first."

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