New research explains repeated infection by some viruses

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New research conducted at the Oregon Health & Science University Vaccine and Gene Therapy Institute explains how a virus that has already infected up to 80 percent of the American population can repeatedly re-infect individuals despite the presence of a strong and long-lasting immune response. The research involves cytomegalovirus (CMV), which infects 50 percent to 80 percent of the U.S. population before age 40. Details of the new findings are printed in this week's online edition of the journal *Science*.

For most people, CMV infection goes undetected and they do not become seriously ill. However, in vulnerable populations with weaker immune systems, such as developing and newborn infants, organ donor recipients and human immunodeficiency virus (HIV) patients, CMV poses a very serious and potentially deadly risk. Some 8,000 children suffer disabilities caused by CMV each year.

"CMV is one of a few virus types that can efficiently re-infect individuals who are already persistently infected by this virus," explained Louis Picker, M.D., associate director of the OHSU VGTI and director of the VGTI's vaccine program. He also serves as director of the Division of Pathobiology and Immunology at the Oregon National Primate Research Center at OHSU.

"When most viruses infect a host, the immune system remembers the disease and protects against re-infection. This is the case with smallpox, seasonal strains of flu and several other viruses. This immune system

reaction is also the reason why vaccines made with weakened or dead viruses work against these pathogens. In the case of CMV, the body's immune system is continuously stimulated by ongoing, low-level persistent infection, but yet CMV is still able to re-infect. This research explains how CMV is able to overcome this immune response so that re-infection occurs."

By studying monkeys at the Oregon National Primate Research Center naturally infected with CMV, researchers demonstrated that CMV re-infection can only take place when the virus is able to evade a key portion of the immune system called CD8+ T cells. These white blood cells, also called "killer T cells," attack and kill infected cells as a part of the body's system. Killer T cells identify infected cells through the presence of molecules on the outside of cells called MHC-I. MHC-I molecules present little snippets of viral proteins to the T cells, thus signaling when a cell is infected. T cells save infected tissues by eliminating infected cells.

"CMV evades these alert systems by making genes that disrupt the MHC-I molecules' ability to communicate an ongoing infection to the T cells. In essence, CMV is able to cutoff an infected cell's call for elimination. This allows CMV to overcome this critical immune barrier during re-infection," explained Klaus Frueh, Ph.D., a senior scientist at the VGTI and a professor of molecular microbiology and immunology in the OHSU School of Medicine.

The results of this study primarily illustrate the significant barriers to creating a vaccine that will prevent CMV infection. However, on a positive note, this research also explains why CMV might be a useful viral vaccine vector. Vaccine vectors are modified viruses that carry genetic material from other pathogens into the body, thus vaccinating against these pathogens. However, because the body also makes an immune response against the vector, current vaccine vectors can only be

used once. Because of their ability to overcome vector-directed immunity, CMV viral vectors may be used repeatedly to stimulate an immune response against a variety of pathogens, including other viruses such as HIV and hepatitis C, but also malaria parasites and tuberculosis bacteria. This research may therefore help aid in the development of such vaccines.

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