Poxvirus' ability to hide from the immune system may aid vaccine design

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The cowpox virus, a much milder cousin of the deadly smallpox virus, can keep infected host cells from warning the immune system that they have been compromised, researchers at Washington University School of Medicine in St. Louis have found. The scientists also showed that more virulent poxviruses, such as the strains of monkeypox prevalent in Central Africa, likely have the same ability.

The study's authors say the finding will help efforts to design new vaccines for use against cowpox, monkeypox and, if it ever became a concern again, smallpox. Researchers working on the next generation of poxvirus vaccines are hoping to minimize the risk of vaccination and to make the vaccines protective against a broader range of viruses.

"Poxvirus vaccines are cross-protective, meaning that immunization from one poxvirus appears to confer protection from other poxviruses, but there are significant risks associated with adult administration of the current vaccine," says senior author Wayne Yokoyama, M.D., professor of pathology and immunology and of medicine and a Howard Hughes Medical Institute investigator. "There are also efforts underway to see if recombinant poxvirus vaccines can convey protection against a broader range of viruses, including HIV and cytomegalovirus."

In addition, the finding is likely to help scientists understand why one strain of poxvirus is more dangerous than another. The results appear Nov. 15 in *Cell Host and Microbe*.

Three decades ago, doctors eliminated the deadliest poxvirus, smallpox, using another poxvirus, vaccinia, as a vaccine. But a few smallpox samples remain in government facilities in the United States and Russia, and those samples have led to concern that terrorists might try to obtain smallpox and use it in a bioterror attack.

Additionally, other species of poxvirus continue to be sources of human disease and, occasionally, deaths. Outbreaks of cowpox, which Edward Jenner used to demonstrate the concept of vaccination in the late 1700s, still occur. In addition, multiple outbreaks of the monkeypox virus, which can cause smallpox-like disease in humans, have occurred in Africa and the United States in the past decade.

To help clinicians better prepare for the possibility of a new natural poxvirus outbreak or a bioterror attack using a poxvirus, Minji Byun, a graduate student in Yokoyama's laboratory, led a laboratory study of interactions between the cowpox virus and the immune systems of mice. Byun collaborated with Xiaoli Wang, M.D., Ph.D., instructor in the laboratory of Ted Hansen, Ph.D., professor in the Department of Pathology and Immunology. The research was supported in part by the Midwest Regional Center of Excellence in Biodefense and Emerging Infectious Diseases Research (MRCE), a multi-institutional research center anchored at Washington University School of Medicine.

Normally the immune system in mice and humans can learn of a viral invasion through a group of molecules known as the major histocompatibility complex (MHC) class I. Because these molecules sit on the surfaces of cells and display samples of proteins from inside the cells, they act as identification badges, in effect telling immune system sentinels, "here's what I'm made of." When immune T cells see virus-derived protein fragments in a cell's MHC class I display, they assume it's been infected and initiate an immune system attack.

But Byun and her colleagues found that cowpox was preventing MHC class I from ever getting to the surface of infected cells. They linked the suppression to a cowpox virus protein, CPXV203, showing that it binds to MHC class I. This binding yanks MHC class I off course by targeting it to the cellular recycling machinery. Once in the recycling loop, MHC class I cannot escape to the cell surface.

"Other viruses have similar strategies for immune system evasion, but this is the first study showing that the poxviruses that are most closely related to smallpox virus can use this approach," says Byun.

A search of the genomes of monkeypox virus revealed a similar protein in the more virulent family of virus strains found in Central Africa. But the less virulent strains active in Western Africa tend to have truncated versions of the proteins similar to CPXV203, leaving them unable to act on MHC class I.

When researchers eliminated the CPXV203 gene and infected mouse cells with the modified cowpox virus, they found it still was able to suppress the appearance of MHC class I on infected cell surfaces, but not as thoroughly.

"There's likely another viral mechanism that produces the same result," Byun speculates. "But it has to be acting on MHC class I in a different way because a search through the cowpox genome failed to reveal any other viral proteins with the same key module as CPXV203."

Pharmaceutically blocking CPXV203 and other similar immune evasion proteins may be tough, according to Yokoyama, because that would disrupt an important natural protein recycling process, potentially causing significant side effects. He believes the finding is more likely to be useful to vaccine scientists. Many vaccines are composed of weakened forms of the microbes they protect against, and the modified

cowpox lacking CPXV203 is likely less virulent.

Yokoyama plans additional studies of poxvirus-immune system interaction in live mice.

Source: Washington University in St. Louis