

Deadly monkeypox virus might cause disease by breaking down lung tissue

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Monkeypox causes infectious pustules as seen in this four-year old Liberian infected with the virus. Credit: Photo courtesy CDC's Public Health Image Library

A new study of an exotic, infectious virus that has caused three recent outbreaks in the United States reveals clues to how the virus might damage lungs during infection. The findings also suggest possible new ways to treat lung diseases in humans.

Not only does the infection from monkeypox virus increase production of proteins involved in [inflammation](#), but it decreases production of proteins that keep lung tissue intact and lubricated. The findings appear in an upcoming issue of *Molecular & Cellular Proteomics*.

"Going into this study, we thought monkeypox caused disease primarily

by inducing inflammation in the lung, and that leads to pneumonia," said lead author Joseph Brown, a systems biologist at the Department of Energy's Pacific Northwest National Laboratory. "We were surprised to see how badly the virus wrecked the structural integrity of the lungs."

The study was funded by the National Institute of Allergy and Infectious Diseases and the National Center for Research Resources, both part of the National Institutes of Health; the Department of Defense; and Battelle.

Collaborating with virologist Scott Wong, Ryan Estep and others at the Oregon Health & Science University's Vaccine and Gene Therapy Institute in Beaverton, Ore., Brown and the PNNL team examined how the virus affected the collection of proteins found in lung fluid from macaque monkeys at OHSU. The monkeys were part of an ongoing study of monkeypox infection at OHSU's Oregon National Primate Research Center in Beaverton.

Monkeypox and smallpox are closely related viruses that cause contagious pustules in humans, though monkeypox is less dangerous. However, monkeypox is as bad for monkeys as smallpox is for people, making it a good model for human smallpox disease. The study helps researchers better understand both monkeypox and smallpox infection.

"If researchers confirm similar events in people, doctors might be able to give surfactants -- lubricating chemicals that aid in gas exchange -- to help the lung function. And the findings could lead to new areas of pulmonary studies in general -- bronchitis or emphysema, lung transplants, the flu," said PNNL co-author Josh Adkins.

The new pox on the street

Monkeypox infections in humans have been on the rise since smallpox

was eradicated in the late 1970s. Up to 10 percent of those infected with monkeypox die of the disease. Monkeypox can be caught from infected rodents, pets and monkeys. Although mainly found in Africa, the first documented infection in the United States occurred in 2003, likely from imported pet prairie dogs.

Researchers attribute the rise of monkeypox infections to the end of smallpox vaccinations, which provided protection against monkeypox due to the similar nature of the two pox viruses. The smallpox vaccine is based upon yet another pox virus called vaccinia, which usually doesn't cause symptoms in people.

A better understanding of how monkeypox causes disease could help doctors manage outbreaks, which will likely continue to occur. Findings about monkeypox infection will also provide insight into smallpox, which is considered a potential bioterrorism agent.

Few studies exist that look at how monkeypox infection damages the lungs. Because symptoms in macaques and humans are so similar, researchers at the OHSU's Primate Center infected macaques with the monkeypox virus and followed the course of infection in the lungs of individual animals. To do this, the OHSU team washed the lungs of infected monkeys with a saline solution and sent the washes to PNNL for protein analysis. The complement of proteins produced by lung tissue before and during infection would indicate how the lungs are responding to the virus.

Immunity and structure

Using cultured cells, the team first verified that infected cells did indeed release proteins that could be detected without damaging the cells. Then the team took samples of a lung wash from four macaques as healthy controls. Next, they infected two of the four with monkeypox virus and

the other two with the nearly symptomless vaccinia virus. They took additional washes every few days for up to seven weeks.

After prepping the saline sample at the primate facility in Oregon, the OHSU team sent non-infectious samples to EMSL, DOE's Environmental Molecular Sciences Laboratory on the PNNL campus, where the PNNL researchers measured and identified as many of the proteins in the samples as they could using proteomics instruments. They compared the infected samples to healthy samples to see whether the level of proteins rose or fell.

Early in infection, monkeypox and vaccinia viruses both stimulated an immune response, they found, ratcheting up production of proteins associated with inflammation. However, the monkeypox-infected lungs also showed a distinct decrease in some proteins -- proteins involved in metabolism, structural proteins that serve as I-beams and cross-beams of [lung tissue](#), and finally surfactant proteins, which provide lubrication and help with oxygen exchange.

A couple weeks into infection, the vaccinia infection wound down and the inflammatory [protein](#) production returned to normal levels. Inflammatory proteins also decreased over time in the monkeypox infected lung fluid samples, but the structural proteins continued to stay low.

"Our results suggest that inflammation contributes to disease but it may not be the main component. Interfering with the structural proteins may play a major role," said Brown.

Culture and virus

The researchers found similar trends with the cultured cells. This suggested that some aspects of monkeypox infection can be studied in

test tubes. However, the animal studies provided novel insights into important physiological details.

In addition, the team directly detected viral proteins in the lung fluid samples. Usually, scientists need to use antibodies to detect viral proteins because there are so few of them swimming in a sea of host proteins. In this case, monkeypox produced 200 proteins to the macaque's estimated maximum of 46,000.

Ultimately, this type of research could have wider implications than viral infection. "This study serves as a great reference for pulmonary diseases," said Adkins. "It opens up the doors for other [lung](#) fluid studies."

More information: Joseph N. Brown, Ryan D. Estep, Daniel Lopez-Ferrer, Heather M. Brewer, Theresa R. Clauss, Nathan P. Manes, Megan O'Connor, Helen Li, Joshua N. Adkins, Scott W. Wong, and Richard D. Smith, Characterization of macaque pulmonary fluid proteome during monkeypox infection: dynamics of host response, *Mol Cell Proteomics* [www.mcponline.org/content/earl ... 8/24/mcp.M110.001875](http://www.mcponline.org/content/earl...8/24/mcp.M110.001875)

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