Poxviruses defeat antiviral defenses by duplicating a gene

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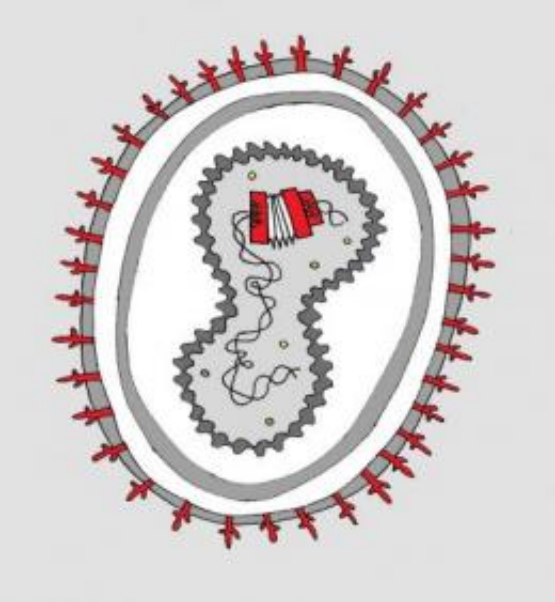

This is a depiction of the poxvirus vaccinia in the adaptive process by which it undergoes gene expansions, mutations, and contractions, allowing it to defeat host immune defenses. A study in Cell, led by Nels C. Elde, Ph.D., of the University of Utah Department of Human Genetics, has shed light on how viruses evolve to fight the immune defenses of host organisms. Credit: Elisabeth Bentz

Scientists have discovered that poxviruses, which are responsible for smallpox and other diseases, can adapt to defeat different host antiviral defenses by quickly and temporarily producing multiple copies of a gene that helps the viruses to counter host immunity. This discovery provides

new insight into the ability of large double-stranded DNA viruses to undergo rapid evolution despite their low mutation rates, according to a study published by University of Utah researchers in the Aug. 17, 2012, issue of *Cell*.

Poxviruses are a group of DNA-containing viruses that are responsible for a wide range of diseases in both humans and animals, including smallpox. Unlike smaller RNA-containing viruses, such as those that cause influenza and HIV, which are able to evade host immune responses through rapid mutation, poxviruses have larger genomes and low mutation rates and little is known about their adaptive strategies against host defenses.

"Poxviruses encode a variety of genes that help them to counter host immune defenses and promote infection," says Nels Elde, Ph.D., assistant professor of human genetics at the University of Utah School of Medicine and first author on the study. "Despite ample evidence that the poxvirus genome can undergo adaptive changes to overcome evolving host defenses, we still don't know that much about the mechanisms involved in that adaptation."

To determine mechanisms of adaptation, Elde and his colleagues studied the vaccinia virus, a type of poxvirus best known for its role as the vaccine used to eradicate smallpox. Previous research has shown that vaccinia virus encodes two genes, known as K3L and E3L, which inhibit host defenses that normally block viral infection. In this study, Elde and his colleagues started with a strain of vaccinia virus that had been altered to delete the E3L gene and repeatedly propagated this E3L-deficient strain in human cells to see how well the virus would replicate. They found that this E3L-deficient strain was quickly able to increase infectious virus production by selectively increasing the number of copies of the K3L gene in its genome.

"This highly specific and rapid gene amplification was unexpected," says Elde. "Our studies show that increasing K3L copy number leads to increased expression of K3L and enhanced viral replication, providing an immediate evolutionary advantage for those viruses that can quickly expand their genome."

Elde and his colleagues also found that, in addition to K3L copy number amplification, some of the E3L-deficient vaccinia strains also acquired a mutation consisting of a single amino acid substitution in the K3L gene. Both the mutation-bearing and multicopy K3L viruses displayed improved viral fitness, or ability to replicate in the host environment, compared to wild-type vaccinia virus. The emergence of this beneficial amino acid substitution suggests that increasing K3L copy number facilitated the appearance of the variant by providing additional mutational targets, despite the virus' otherwise low mutation rate.

"We were able to demonstrate at least two strategies by which poxviruses are able to adapt diverse mechanisms of host immunity," says Elde. "Our observations reveal that, while poxviruses do undergo gene mutation, their first response to a new, hostile host environment can be rapid gene expansion. We also found evidence that the virus genome can contract after acquiring an adaptive mutation, thus alleviating the potential trade-off of having a larger genome, while leaving a beneficial mutation in place."

Although smallpox was officially eradicated by the World Health Organization in 1980, concerns about the use of smallpox as a bioterrorism agent have spurred renewed interest in the study of vaccinia and other poxviruses. In addition, poxvirus infections, such as monkeypox, can be transmitted from animals to humans and the adaptive strategies of poxviruses may be relevant for other infectious organisms.

More information: *Cell* paper: “Poxviruses deploy genomic accordions to adapt rapidly against host antiviral defenses”

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