Halting the hijacker: Cellular targets to thwart influenza virus infection

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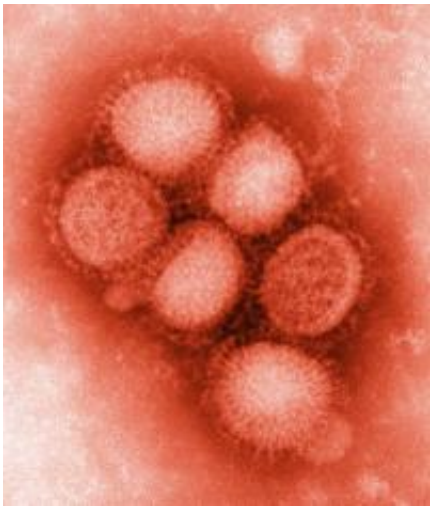

An influenza strain. Image: Centers for Disease Control

The influenza virus, like all viruses, is a hijacker. It quietly slips its way inside cells, steals the machinery inside to make more copies of itself, and then—having multiplied—bursts out of the cell to find others to infect.

Most drugs currently used to treat influenza are designed to attack the virus, to render it incapacitated. But influenza viruses are sneaky, capable of mutating to avoid destruction by the drug.

In a comprehensive new study published today in the journal *Cell Host*

and Microbe, the University of Wisconsin-Madison's Yoshihiro Kawaoka and a team of researchers have set the stage for an entirely different approach. They have revealed methods for thwarting the hijackers by shutting down the cellular machinery they need, like cutting the fuel line on a bank robber's getaway car.

The findings will aid in the selection and development of new drugs that target the cellular machinery viruses rely on—rather than attacking the virus itself—lowering the chances it will mutate and become resistant to the drug.

"Whenever patients are treated with a drug, viruses are under selective pressure," says Kawaoka, a professor in the UW-Madison School of Veterinary Medicine. "In 2007, a (drug) resistant influenza virus emerged and within one-and-a-half years, it spread worldwide."

By combing through the cellular machinery, collaborating scientists at UW-Madison and several institutions in Japan identified 1,300 host cell proteins the virus may use to bind to and enter the cell, travel around inside the cell, replicate (make more of itself), or exit the cell.

While several other studies have performed human genome-wide screens to look for host cell proteins that interact with influenza virus, Kawaoka's study is the first to take it well beyond identification of potential targets.

One-by-one, the research team tested each protein to see whether eliminating it from human cells grown in the lab, using a technique called gene silencing, interfered with the infectivity of the virus. At the same time, the researchers assessed how harmful the approach was to the cells.

Negative, unwarranted side effects are one risk of targeting host proteins

with drugs, so Kawaoka wanted to make sure the approach was not toxic.

The team identified 91 potential host cell targets, which they called their "top hits." These were proteins that could be reduced inside cells leading to lower concentrations of infecting virus but little to no cell death.

Using these candidates, the researchers then mapped each protein to its role in the viral infection cycle, providing a much greater understanding of how an influenza virus works inside cells and a platform for further exploration.

"The information described in this paper will be of great value to those who are interested in developing antiviral compounds that are targeted, but reduce virus titers," Kawaoka, also on the faculty at the University of Tokyo, says. "Also, these data are of considerable interest to basic researchers."

Going further, the team combed through drug databases to identify compounds that may suppress the cellular targets and shut down influenza virus infection. In doing so, they came up with several possible drugs—and some surprises.

Two of the compounds inhibited host cell proteins the scientists would never have suspected as targets for antivirals, based on what is currently known about them. Several clinical drugs already exist for one of these targets and are already in advanced clinical testing for other conditions, demonstrating their therapeutic potential.

The research team continues to study their top hits, to assess their drug development potential. Kawaoka's overall goal is to identify strategies to either prevent or treat potentially lethal viral infections. The World Health Organization estimates there are 3-to-5-million cases of influenza worldwide each year, with as many as 500,000 deaths.

Kawaoka doesn't yet know how many host proteins may pose as good potential drug development targets.

"That is difficult to say," he says. "But, we are working on our top 20 for now."

Provided by University of Wisconsin-Madison