Fred Hutch Researchers Discover an Unknown Soldier in Defense Against Viruses

A gene better known for its role in cancer progression also plays a surprising role in mounting an immune defense against Zika virus.

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When a nasty bug infects a cell, the cell sends out riders called interferons that, like Paul Revere, warn the other cells: A virus is coming! A virus is coming!

Interferons bind to receptors on the cell's surface, starting a message chain that carries the warning into the cell's nucleus. The alarm activates interferon-stimulated genes, or ISGs, which produce antiviral proteins — a molecular militia to fight the invader.

A recent study in the journal PNAS from the lab of Julie Overbaugh, PhD, reveals when the Zika virus invades, interferon musters the usual militia, but the alarm also is regulated by a gene with a previously unknown antiviral function that plays an important role in cellular defense.

Dr. Alexandra Willcox entered the Medical Scientist Training Program at the University of Washington in 2019 and is now in her third year of medical school after earning her PhD last March.Courtesy of Fred Hutch News Service/Robert Hood

Surprisingly, this soldier doesn't take orders from interferon like the rest of the militia, but rather helps the orders get through, according to the study, which was led by then graduate student, Alexandra Willcox, PhD, with colleagues at Fred Hutch Cancer Center.

The discovery wasn't what Willcox was expecting, but her out-of-the-box solution to a molecular mystery has implications for the treatment not only of Zika virus but of other viruses and even cancer.

"It was one of the hardest projects that any graduate student in my lab has had," said Overbaugh, who holds the Endowed Chair for Graduate Education and specializes in HIV, the retrovirus that causes AIDS. "Alex really stuck with this project through many twists and turns."

A virus that no longer makes headlines but still makes trouble

Before 2015, Zika was a relatively unknown virus spread by mosquitoes until it became a global health emergency during an outbreak in Brazil, with resulting spread to almost every country in the Western Hemisphere.

Though Zika virus disease was previously thought to be usually mild, it was discovered during that outbreak that infection during pregnancy can cause birth defects including microcephaly (smaller than expected brain and skull size), impaired brain development, feeding problems, hearing loss, vision problems, seizures and death.

Zika virus can also trigger Guillain–Barré syndrome, a rare neurological disorder in which a person's immune system mistakenly attacks nerves that carries signals from the brain and spinal cord to the rest of the body, potentially causing symptoms ranging from brief weakness to life-threatening paralysis.

Five percent of pregnant women with a confirmed Zika virus infection in the United States territories, including Puerto Rico, went on to have a baby with a related birth defect, according to a 2017 report from the Centers for Disease Control and Prevention.

Though Zika virus disappeared from the headlines as the epidemic subsided, Willcox remained interested in the virus, which is considered a dangerous, seasonal disease that can return repeatedly to countries that have the Aedes aegypti mosquitoes, which spread the virus.

"It's still around and it's only going to come back and cause worse outbreaks in the future," said Willcox, who began studying the virus as an undergraduate student at the University of North Carolina at Chapel Hill. "So that just kind of scared me and I found that very interesting."

A CRISPR screen reveals an unknown soldier

Willcox entered the Medical Scientist Training Program at the University of Washington in 2019 and is now in her third year of medical school after earning her PhD last March.

When she joined the Overbaugh Lab in the Human Biology Division of Fred Hutch, she seized on the chance to study Zika virus.

Her assignment: identify the important genes that activate and target the virus when interferon sounds the Zika virus alarm.

It was particularly challenging because the lab at that time had limited experience both in studying Zika virus and in using a CRISPR-Cas9 gene-editing knock-out screen, Overbaugh said.

This versatile, Nobel Prize-winning tool can help scientists find antiviral genes by knocking them

out individually and seeing how their absence affects the cell's ability to defend against the virus.

An enzyme called Cas9 snips DNA at precise locations and CRISPR guide molecules deliver the Cas9 snippers to the gene that researchers want to knock out. When the cell repairs the break, it's usually not good enough to restore the gene's function, which knocks it out.

To screen for host genes of interest, the CRISPR guides for each target gene are combined in a library that can be applied to a population of cells so that the Cas9 snippers knock out just one gene in each cell. The whole population can then be studied in a single experiment that exposes all the cells to the same conditions.

Willcox added interferon to muster the cells' defenses and then infected them with Zika virus. If Zika virus infected a cell better, it indicated that the knocked-out gene in that cell was important to its defense.

An unexpectedly important gene popped out of her screen called AMOTL2, which is involved in cell structure and signaling. It's not generally known as an antiviral gene, but it is associated with cancer progression.

The overlap with cancer wasn't so surprising because most antiviral genes have other functions and some viruses, such as human papillomavirus, cause cancer.

But there was something peculiar about AMOTL2: unlike the usual militia called out to fight an infection, AMOTL2 isn't regulated by interferon; rather it appears to regulate the interferon response itself, including all the downstream genes of the militia.

It was such an unexpected result that Willcox didn't know what to make of it.

"At first when we got the gene, we kind of just assumed it was an ISG and then I spent a while trying to confirm that," Willcox said. "And time and time again, it was just not coming up as regulated by interferon. And that was kind of frustrating because we didn't really know what to think or where to go from there. I needed to think outside the box a little bit to figure it out."

Muffling the alarm

Someone on her PhD thesis committee suggested that rather than trying to confirm whether it is regulated by interferon, Willcox should just figure out what it's doing to aid in the defense of the cell.

If interferon is like a bugler sounding the infection alarm to muster the troops (ISGs), but AMOTL2 isn't an ISG following the bugler's orders, then what is it doing?

Willcox hypothesized that AMOTL2 might be involved sooner in the process — what researchers call "upstream" in the flow of events that leads to ISG production.

She discovered that when AMOTL2 is functioning normally, a protein called Stat1 gets activated and efficiently relays the interferon alarm to the cell's nucleus so it can start cranking out the militia.

But when AMOTL2 is knocked out, a crowd of inactivated Stat1s accumulates in the cell, hanging around with nothing to do, which muffles interferon's alarm and results in reduced production of ISGs to fight the infection.

In other words, AMOTL2 makes sure that interferon's orders get through so the cell can turn out the militia.

Not just Zika virus

Overbaugh and Willcox knew that their findings would be stronger for publication if they could demonstrate that AMOTL2 played a similar role in other viruses.

But time was running out for Willcox to do that herself. She completed the PhD portion of the physician-scientist program in March and now she had to finish medical school to earn her MD.

They got some help from colleagues in two labs: Adam Geballe, MD, in the Human Biology Division, who was also on Willcox's PhD committee, and members of the Harmit Malik Lab, in the Basic Sciences Division.

They tested her hypothesis that AMOTL2's role in viral defense wasn't specific to Zika and both came up with promising results. Despite long hours in the clinic, Willcox continued to be involved with the collaborators in experimental design and pushed to see this project through.

One of the confirmatory experiments was complete enough to include in the study.

Study co-author Tamanash Bhattacharya, PhD, a postdoctoral fellow in the Malik Lab, confirmed the same antiviral effect of AMOTL2 in a mosquito-borne virus often studied in biological research called Sindbis.

Willcox was thrilled to see that Bhattacharya found the same effect in a different virus, which strengthened the study.

"I was crossing my fingers for sure," she said.

A better understanding of how our innate immune system combats Zika virus could lead to better ways to control it, but the discovery has broader implications.

It suggests that AMOTL2's antiviral function isn't specific to Zika virus but plays a more general role whenever interferon is involved in fighting viruses or cancers.

“It’s not just Zika virus,” Overbaugh said. “It could be anything that interferon regulates.”

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