A Deadly Virus Carried by Fruit Bats

Intrigued by how viruses jump from animals to humans, Hector Aguilar-Carreno studies Henipaviruses, which have caused deadly outbreaks of Nipah virus.

Featured

Hector Aguilar-Carreno
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by Jackie Swift

As human populations have increased around the world, people have increasingly encroached on wildlife habitats. Often the animals lose in these encounters, but for humans there has also been a price to pay: previously unknown, deadly diseases that have jumped

from animals to humans. Ebola is one of the most well-known, but there are others—viruses that have lived with their animal hosts for thousands of years in a carefully orchestrated balance where neither host nor virus can completely destroy the other.

When these viruses finally have the chance to infect humans, they cause high mortality rates. "Killing the host is not a good thing for the virus," says Hector Aguilar-Carreno, Microbiology and Immunology. "Most likely the viruses that have been living with humans for thousands of years, like influenza, have co-evolved with us. They know how to replicate within us and spread from human to human without killing us, for the most part. But a virus that did not evolve with us, one that we've just encountered recently, can't do that yet."

Nipah Virus Outbreaks

Aguilar studies Henipaviruses, a genus of the family of viruses known as *Paramyxoviridae.* Common human illnesses such as measles, mumps, and parainfluenza are caused by viruses from this family, but until very recently the Henipaviruses, carried by fruit bats, were not known to infect humans. That changed in 1999 when the first outbreak of Nipah virus occurred in Malaysia and Singapore. Other outbreaks followed over the course of the next two decades in Bangladesh, the Philippines, and India in the summer of 2018. "Nipah virus kills from 40 to 100 percent of infected individuals," Aguilar says. "All of these outbreaks were eventually contained. They happened in remote villages, but if even one of those infected people had gotten into a big city with a dense human population, it may have been a completely different story."

Studying How the Nipah Virus Infects

To understand and counter the threat of Henipaviruses, Aguilar and his lab study how the Nipah virus, and its cousin the Hendra virus, enter and infect a cell. "We look at the mechanisms of that entry," Aguilar says. "It's very clever. The virus has an attachment protein and a fusion protein that act in concert, kind of like a burglary, to get inside the cell."

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The researchers discovered the relevant receptors on the surface of a cell—ephrinB2 and ephrinB3—to which the Nipah virus attachment protein binds. They also pinpointed the

mechanism by which the attachment protein triggers the fusion protein to open and insert a spike through the cell's membrane, thereby fusing the virus and the cell membranes together. Once fused, the virus' RNA can move inside the cell cytoplasm and replicate thousands of copies of itself.

"Something uncommon about Nipah virus is that it fuses the infected cell together with uninfected cells around it," says Aguilar. "It forms a syncytium, a fusion of up to hundreds of cells. That's how it gains additional machinery to make more of itself."

Since Nipah virus requires the highest-level biosafety lab, which Cornell does not have, Aguilar collaborates with the National Institutes of Health's Rocky Mountain Laboratory in Hamilton, Montana and the Center for Disease Control in Atlanta, Georgia to work with the live virus. Much of his research, however, does not require the full virus. "We do 99 percent of our work right here at Cornell in my lab," he says. "We've engineered ways to look at viral entry and viral assembly without using the full, live virus."

The researchers create viral-like particles by removing a part of the virus, the infectious genetic material. Then they study the part that remains. They also engineer pseudoviruses by putting a piece of a dangerous virus like the Nipah virus glycoproteins onto another virus that is not virulent. This allows them to investigate the attachment and fusion proteins of the Nipah virus without having to worry about the actual Nipah virus infecting a cell. "We make mutations to the proteins as well," Aguilar explains. "The mutations help us determine which part of the protein has a certain effect. So, if I mutate a certain part and the protein can no longer carry out a particular action, then I know that part must be important for that action."

The DARPA Project on Henipaviruses

Aguilar and his lab are part of a large project, headed by Raina Plowright at Montana State University that recently received a grant for about $10 million from the United States Defense Advanced Research Projects Agency (DARPA). Involving at least a dozen labs, the DARPA project will look at Henipaviruses carried by fruit bat populations around the world. The bats carry the viruses without becoming ill themselves and transmit the virus through their urine, saliva, and feces. Aguilar's collaborators will take urine samples from fruit bats and sequence them to obtain the RNA sequences of Henipaviruses the bats are carrying. Then those sequences will be sent to Aguilar's lab where he and his colleagues will analyze the likelihood of a particular virus leaping into humans.

"We know that Nipah and Hendra viruses are two of around 20 discovered Henipaviruses that have the potential to jump into humans. We want to see how closely related these other Henipaviruses are to Nipah and Hendra," Aguilar explains. "We will look at the RNA sequences, but we also have several functional assays we'll use. For example, we'll look at

whether they bind to the same receptors on the cell surface of their hosts as Nipah and Hendra; whether they can fuse with the cell in the same way; and whether they can enter the cell and assemble there to make new viruses."

Working on a Vaccine, Now

In the end, all the data generated by Aguilar's lab and others will be analyzed by computer modelers to generate a worldwide scenario of the odds that a particular virus will spill over to humans. No matter the results, Aguilar is also working on the possibility of a vaccine for the Nipah virus and its relatives. Using virus-like particles, he and his laboratory and collaborators are testing whether these are capable of priming the immune system without infecting the host. So far, the results look promising.

Aguilar has respect for the viruses he studies. "They are extremely remarkable," he says. "You can consider them either the simplest form of life, or not really alive at all. They are basically a piece of genetic material. The Nipah virus, for example, is just six genes. A human being has over 20,000 genes, yet these six genes are able to overcome a whole human being. It's amazing to see this, to discover how this happens."

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