'Defective' virus surprisingly plays major role in spread of disease

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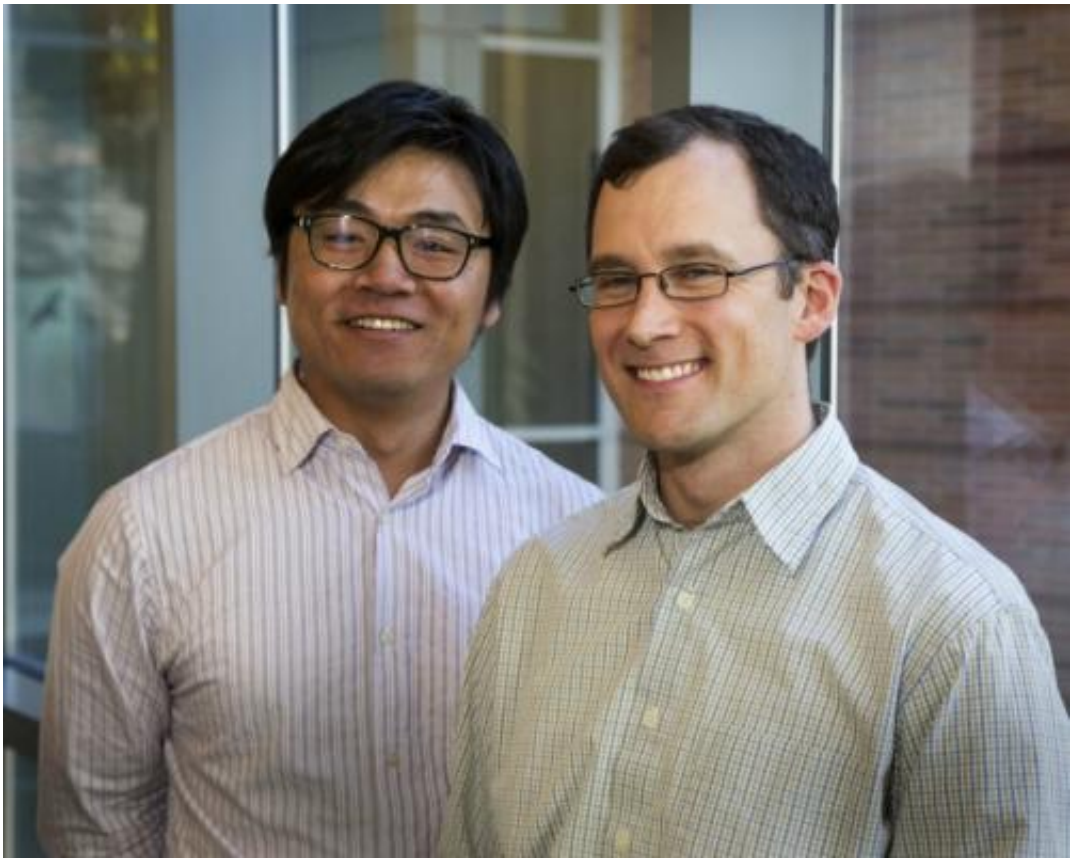

Ruian Ke and James O. Lloyd-Smith. Credit: Reed Hutchinson/UCLA

(Medical Xpress)—Defective viruses, thought for decades to be essentially garbage unrelated to the transmission of normal viruses, now appear able to play an important role in the spread of disease, new research by UCLA life scientists indicates.

Defective viruses have genetic mutations or deletions that eliminate their essential viral functions. They have been observed for many human pathogens and are generated frequently for viruses that have high mutation rates. However, for some 40 years, it was believed that they were unimportant in natural settings.

In findings published Feb. 28 in the journal PLoS Pathogens, UCLA scientists and their colleagues report for the first time a significant link between a defective virus and an increased rate of transmission of a major disease.

"The idea has always been that defective viruses are either meaningless or detrimental," said James O. Lloyd-Smith, a UCLA assistant professor of ecology and evolutionary biology and the senior author of the research. "We have found the opposite of that—that the defective virus is actually helping the normal, functional virus. This finding is bizarre and hard to believe, but the data are the data."

"We have shown that the defective virus not only transmits with the virus but increases the transmission of the functional virus," said Ruian Ke, a UCLA postdoctoral scholar in the department of ecology and evolutionary biology and the lead author of the study.

Defective viruses cannot complete their life cycle on their own, but if they're able to get into the same cell with a non-defective virus, they can "hitchhike" with the normal virus and propagate, Lloyd-Smith said. Biologists had thought that defective viruses interfered with normal versions of the virus, "clogging up the gears of viral replication," he said.

The life scientists studied DENV-1, one of four known types of the dengue virus that infect humans. Dengue viruses are transmitted by several species of mosquitoes and cause dengue fever, which is characterized by fever, joint pain and a skin rash similar to measles.

Dengue hemorrhagic fever, a more severe form of dengue infection, can cause death. The dengue virus infects between 50 million and 100 million people each year in Southeast Asia, South America, parts of the United States and elsewhere.

The life sciences team—which also included John Aaskov, a virologist and professor of health at Australia's Queensland University of Technology in Brisbane, and Edward Holmes, a professor of biological sciences at Australia's University of Sydney—found that the presence of a defective DENV-1 virus may have led to large increases in dengue fever cases in Myanmar in 2001 and 2002, when that country experienced its most severe dengue epidemics on record.

The scientists describe when and how the defective "lineage," or series of very closely related defective DENV-1 viruses, emerged and was transmitted between humans and mosquitoes in Myanmar, as well as what the public health implications are.

For the study, Ke designed a mathematical model to analyze the data to learn how the defective DENV-1 virus interacted with the normal virus. Aaskov and Holmes collected genetic sequences from from 15 people in Myanmar sampled over an 18-month period, all of whom were infected with the DENV-1 virus and nine of whom were also infected with the defective version.

Ke discovered that the lineage of defective viruses emerged between June 1998 and February 2001 and that it was spreading in the population until at least 2002. (The following year, the lineage appeared on the South Pacific island of New Caledonia, carried there by either a mosquito or a person.) The scientists analyzed the genetic sequences of both the defective and normal dengue viruses to estimate how long the defective virus had been transmitting in the human population.

"We can see from the gene sequence of the defective version that it is the same lineage and is a continued propagation of the virus," said Lloyd-Smith, who holds UCLA's De Logi Chair in Biological Sciences. "From 2001 to 2002, it went from being quite rare to being in all nine people we sampled that year; everybody sampled who was getting dengue fever was getting the defective version along with the functional virus. It rose from being rare to being very common in just one year."

Most surprisingly, Lloyd-Smith said, the combination of the defective virus with the normal virus was "more fit" than the normal dengue virus alone.

"What we have shown is that this defective virus, which everyone had thought was useless or even detrimental to the fitness of the functional virus, actually appears to have made it better able to spread," he said. "Ruian [Ke] calculated that the defective virus makes it at least 10 percent more transmissible, which is a lot. It was spreading better with its weird, defective cousin tagging along than on its own.

"This study has shown that the functional virus and defective virus travel in unison. The two transmit together in an unbroken chain, and that's not just a matter of getting into the same human or the same mosquito—they need to get into the same cell inside that human or mosquito in order to share their genes and for the defective version to continue 'hitchhiking.' We are gaining insights into the cellular-level biology of how dengue is infecting hosts. It must be the case that frequently there are multiple infections of single cells.

"Ruian showed the defective virus appeared one to three years before these major epidemics," Lloyd-Smith added. "One could imagine that if you build an understanding of this mechanism, you could measure it, see it coming and potentially get ahead of it."

Might defective viruses play a role in the transmission of influenza, measles and other diseases?

"There are a few signs that this phenomenon may be happening for other viruses," Lloyd-Smith said. "We may be cracking open the book on the possible interactions between the normal, functional viruses and the defective ones that people thought were just dead-ends. These supposedly meaningless viruses may be having a positive impact—positive for the virus, not for us. There is great variation, year to year, in how large dengue epidemics are in various locations, and we don't understand why. This is a possible mechanism for why there are large epidemics in some years in some places. We need to keep studying this question."

The research points to implications for how mutations might allow a new non-human virus to become a human virus.

"Different strains of a virus with different genetic properties may be interacting more frequently than we thought," said Lloyd-Smith, who studies how ecology, evolution and epidemiology merge to drive the emergence of new pathogens, including new strains with important properties like drug resistance.

Why would a defective virus increase transmission of a disease?

Lloyd-Smith offers two hypotheses. One is that the presence of the defective virus with the functional virus in the same cell makes the functional virus replicate better within the cell by some unknown mechanism. "It might give the virus a bit of flexibility in how it expresses its genes and may make it a bit more fit, a bit better able to reproduce under some circumstances," he said.

A second idea is that the defective virus may be interfering with the

disease-causing virus, making the disease less intense; people then have a milder infection, and because they don't feel as sick, they are more likely to go out and spread the disease.

"Normally, biologists test for how well a virus can replicate in a cell, but what we have shown here is even a genotype that cannot replicate in a cell can have an impact on transmission," Ke said.

In conducting the research, Lloyd-Smith and Ke combined genetic sequence analysis with sophisticated mathematical models and bioinformatics.

Genetic sequencing technology has "exploded," Lloyd-Smith said, providing a wealth of data on genetic sequences of pathogens and the evolution of viruses, leading to major new insights into the transmission of viruses.

"We were able to show that this defective virus transmitted in an unbroken chain across this population for a year-and-a-half," Lloyd-Smith said. "Without gene sequencing, we would not have been able to establish that."

More information: dx.plos.org/10.1371/journal.ppat.1003193

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