MedicalXpress

Structure of Lassa virus protein reveals viral thievery

November 17 2010

A subunit of the Lassa nucleoprotein. The C terminal domain at top and the N-terminal domain at bottom.

Scientists at Emory University and the University of St. Andrews have solved the structure of a key protein from Lassa virus, which is endemic to West Africa and can cause a deadly hemorrhagic fever.

The structure reveals how the virus evades its host's immune system, and how it hijacks infected cells' vital machinery in a process scientists call "cap-stealing." Details of the structure could guide future efforts at antiviral drug discovery and vaccine development.

The results are published in this week's issue of *Nature*.

Lassa virus represents a family of viruses – arenaviruses -- whose natural hosts are rodents and cause hemorrhagic fevers in Africa and South America. New varieties of arenavirus continue to emerge, such as the deadly "Lujo" virus identified recently in Zambia and South Africa.

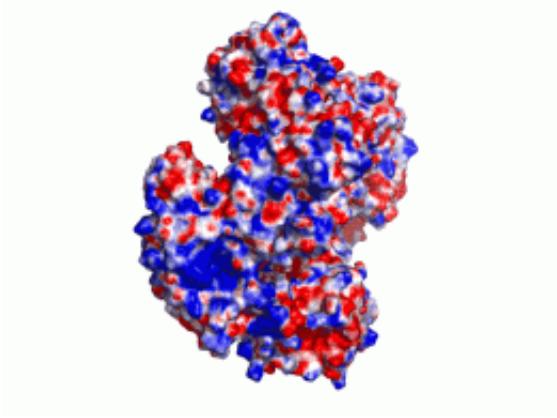
Lassa virus infects 100,000 to 300,000 people every year in West Africa, with an estimated 5,000 deaths, according to the Centers for Disease Control and Prevention. Most people infected have a mild illness, but about 20 percent have a severe multisystem disease with internal bleeding and immune suppression. Around one percent of all infections are fatal. A common complication of infection is deafness.

Lassa virus' NP (nucleoprotein) is the first protein produced after viral infection and the most abundant component of the virus. To study the properties of Lassa virus NP, virologists at Emory collaborated with structural biologists at University of St. Andrews, who examine the details of protein structure with X-rays. The X-ray data was collected at the Diamond Light Source, the United Kingdom's national synchotron facility. The *Nature* paper's co-senior authors are Changjiang Dong, PhD, a Wellcome Trust fellow at St. Andrews, and Yuying Liang, PhD, and Hinh Ly, PhD, both assistant professors of pathology and laboratory medicine at Emory University School of Medicine. The first author is St. Andrews postgraduate student Xiaoxuan Qi.

Human cells can usually detect viral infection with internal alarm systems that sense the presence of viral components, such as viral RNA or DNA. Arenaviruses such as Lassa virus have genomes made of RNA instead of DNA. Because cells send out molecules called interferons to muster the immune system against the virus, many viruses have developed ways to block interferon production.

Based on the X-ray structure, the authors discovered that Lassa virus NP has the ability to chew up RNA molecules. By testing versions of Lassa virus NP with that part of the protein disabled, they confirmed that this property is needed to suppress cells' interferon production.

"What I think is exciting is that we are seeing a new viral mechanism for suppressing the interferon response," Liang says. "This is the first viral protein anyone has found that destroys the RNA molecules that are the triggers for these internal alarms."



The trimeric electrostatic surface of the Lassa nucleoprotein shows the cavity in blue for viral RNA synthesis and in red for immune evasion. The central ring of the trimer is responsible for protection of the viral genomic RNA.

What remains a puzzle is how the virus avoids chewing up cellular and viral RNA indiscriminately, she says.

The authors observed that Lassa NP can form rings by clustering in groups of three. Liang and Ly hypothesize that in a complete virus, the RNA genome is threaded through the three-part ring, with the RNA-chewing region of the protein facing out.

The authors also discovered that a separate region of Lassa virus NP can grip a cap structure normally found on RNA molecules produced by the host cell. This cap must be present at the beginning of all messenger RNAs to tell the cell's protein-production machinery where to start.

"Lassa virus can't make its own cap, so it steals one from the host," Ly says. "Seeing how a virus with only four genes can trick the cell and cause so many problems is a great illustration of efficiency. Each viral gene has to serve multiple functions."

Influenza virus also performs the feat of "cap-stealing," but the influenza virus protein that binds the cap structure does not look like the Lassa virus protein and the cap structure stolen by the flu virus differs from that of Lassa, he says.

Having structural information on Lassa virus NP may help scientists look for antiviral drugs. The only drug available against Lassa virus is ribavirin. Scientists say that how ribavirin works is unclear, and that it is only effective when used early, a significant limitation when Lassa virus infections often take a couple of weeks to become serious.

In Emory laboratories, researchers study individual genes and proteins from Lassa virus, but not the intact virus, because it is classified at the highest level of biosafety concern: BSL-4.

Provided by Emory University

provided for information purposes only.