Juvenile diarrhea virus analyzed

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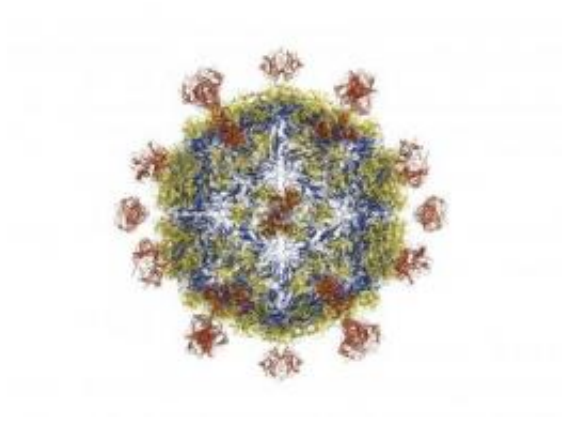

The spiky capsid shell of the astrovirus believed responsible for a form of juvenile diarrhea contains and protects single-strand RNA until it can be delivered to a cell. Credit: Jinhui Dong/Rice University

Rice University scientists have defined the structure -- down to the atomic level -- of a virus that causes juvenile diarrhea. The research may help direct efforts to develop medications that block the virus before it becomes infectious.

The new paper by Professor Yizhi Jane Tao, postdoctoral researcher Jinhui Dong and their colleagues was published in today's online edition of the Proceedings of the National Academy of Sciences.

Tao's Rice lab specializes in gleaning fine details of viral structures through X-ray crystallography and computer analysis of the complex molecules, ultimately pinpointing the location of every atom. That helps

researchers see microscopic features on a virus, like the spot that allows it to bind to a cell or sites that are recognized by neutralization antibodies.

Among four small RNA viruses that typically infect people and animals, Tao said, astrovirus was the only one whose atomic structure was not yet known. First visualized through electron microscopy in 1975, it became clear in subsequent studies that the virus played a role in juvenile -- and sometimes adult -- outbreaks of diarrhea, as the second leading cause after rotavirus. Passed orally, most often through fecal matter, the illness is more inconvenient than dangerous, but if left untreated, children can become dehydrated.

The virus works its foul magic in humans' lower intestines, but to get there it has to run a gauntlet through the digestive tract and avoid proteases, part of the human immune system whose job is to destroy it. (Though one, trypsin, actually plays a role in activating astrovirus, she said.) When the astrovirus finds a target and viral RNA is let loose inside human cells, virus replication starts. If the host's immune system does not do a good enough job in removing the viruses, the malady will run its uncomfortable course in a couple of days.

Rice University postdoctoral researcher Jinhui Dong mounts a protein crystal to an X-ray machine to collect diffraction data. Credit: Jeff Fitlow/Rice University

Astrovirus bears a strong resemblance to the virus that causes hepatitis E (HEV). Tao, an associate professor of biochemistry and cell biology, said she decided to investigate astrovirus after completing a similar study of HEV two years ago. "I was thinking there's some connection between those viruses," she said. "Based on that assumption, we started to make constructs to see if we could produce, to start with, the surface spike on the viral capsid."

The capsid is a hard shell 33 nanometers wide that contains and protects its RNA. It has 30 even tinier spikes projecting from the surface, and each of those spikes may have a receptor-binding site.

Once the atomic structure of the spike was known, finding the receptor site took detective work that involved comparing genomic sequences of eight variants of astrovirus to find which were the best conserved. "Among those eight serotypes, we figured there must be a common receptor, and that should be conserved on the surface," said Dong, the paper's lead author.

In looking for the common receptor, the team found a shallow pocket in the spike that became a prime suspect for receptor binding.

The researchers also discovered the astrovirus may have a sweet tooth. "The size of the pockets suggests that it would most likely bind to sugar molecules, like disaccharides or trisaccharides," Tao said. "It may be that the virus binds to the sugar molecule and that helps it bind to the surface of a target cell."

Finally, the team also determined astrovirus resembles another of the four types of RNA-based viruses, calicivirus, although more remotely than HEV. They suspect astrovirus may be a hybrid, with parts derived

from both HEV and calicivirus. "Clearly, these three are related somehow. It's an interesting point, but we can't determine that relationship based on what we know right now."

What researchers can do is begin to develop a vaccine or antiviral drug that will block astrovirus. "There's already a phase II vaccine (in trials) for HEV, so that gives us hope," Dong said.

"We will certainly work with other labs to identify compounds that can bind to this potential pocket," Tao said. "We can do this computationally. We can screen 50,000 compounds, for example, to see which may bind to the protein with high affinity. Then we can start the optimization procedure."

Provided by Rice University