Chronicle / Lab Book

Untangling a Viral Infection

A host cell enzyme is commandeered by a knot-like structure in flavivirus RNA.

Flaviviruses are resourceful. The agents behind West Nile and dengue fever trick their host’s invader-fighting enzymes into helping the virus infect more cells. HHMI Early Career Scientist Jeffrey Kieft is resourceful too. He’s figured out how these pathogens perform their trickery and devised a potential way to put an end to it.

“Scientists discovered a long time ago that when flaviviruses infect a cell, they produce a subgenomic RNA molecule that is essential for viral infection,” explains Kieft. The molecule, called small flaviviral RNA (sfRNA), is actually created by a host enzyme named Xrn1. Ironically, Xrn1 can help defend the host by destroying foreign RNA. But in this case, it helps the invader attack.

To its credit, Xrn1 manages to chew up most flavivirus RNA, but then it stops, and the fragment that remains is the damage-inflicting sfRNA. Kieft and his team at the University of Colorado Denver characterized the spot on the viral RNA that blocks the enzyme from moving along the foreign RNA. It turned out to be a knot-like fold in the RNA that acts as a blockade.

“Xrn1 is chewing down the RNA, progressing really easily, and it runs into this tangled-up RNA structure and just can’t get by,” explains Kieft. “It can’t figure out how to untie the ‘knot.’”

The scientists also learned that if they disrupt the knot-like structure by changing certain nucleotides in the RNA, Xrn1 can successfully chew through the RNA and prevent production of the pathogenic sfRNA. They published their findings in two papers—one in the April 1, 2014, issue of eLife and the other in the April 18, 2014, issue of Science.

If researchers can find a way to prevent viral RNA from forming the knotty snarl, they will have a treatment for flavivirus diseases. “Now that we’ve got a full picture of the structure and have a model for how it stops Xrn1, we can get serious about trying to target the blockade with small molecules to disrupt its structure,” says Kieft.

— Nicole Kresge

A knot-like fold in flavivirus RNA helps the pathogen trick host cell enzymes.

IN BRIEF

TURBO SPEED
When a fruit fly detects a looming predator, it can launch itself into the air and soar to safety in just a fraction of a second. But what happens if even a fraction of a second is too long? According to scientists at HHMI’s Janelia Research Campus, flies can employ an even quicker escape response that helps them evade their swiftest predators. Janelia Group Leaders Gwyneth Card and Anthony Leonardo and their lab teams recorded the reactions of more than 4,000 flies exposed to a looming dark circle that simulated the approach of a predator. They discovered the flies have two distinct responses: a slow and steady takeoff in which they take time to raise their wings fully, and a quicker, clumsier escape that eliminates this step.

“The fly’s rapid takeoff is, on average, eight milliseconds faster than its more controlled takeoff,” says Card. “Eight milliseconds could be the difference between life and death.”

By monitoring neurons in the flies’ brains, the scientists learned that different neural circuits control the two types of takeoff. Any sort of threat will activate the slow, controlled escape neural circuit. But if the threat is closing in quickly—for example, a swooping damselfly—the speedy escape circuit will kick in and override the slow one.

The findings, published in the July 2014 issue of Nature Neuroscience, help shed light on the neural circuits animals use to select one behavior and override the slow one.

SHARPER IMAGE
A big problem in microscopy is that biological samples bend and distort light in unpredictable ways. The larger and more complex the specimen, the more erratic the light—and the fuzzier the resulting image. To circumvent this obstacle, Janelia Group Leader Eric Betzig created a new microscopy technique that borrows from astronomy and ophthalmology.

Astronomers correct for atmospheric distortion by shining a laser skyward in the direction they plan to observe, and then measuring the distortion of the returning light. Betzig and his colleagues duplicated this process on a smaller scale by figuring out how a tissue sample distorts infrared light. They corrected for aberrations in the returning light with a method ophthalmologists use to adjust for the movement of a patient’s eyes when capturing retinal images.

The techniques allowed Betzig and his colleagues to bring into focus the subcellular organelles and fine, branching processes of nerve cells deep in the brain of a living zebrafish. “The results are pretty eye-popping,” says Betzig, who published the method in the June 2014 issue of Nature Methods.

“We kept on pushing this technology, and it turns out it works,” explains Kai Wang, a postdoctoral fellow in Betzig’s lab. “When we compare the image quality before and after correction, it’s very different. The corrected image tells a lot of information that biologists want to know.”

Y IS HERE TO STAY
The human Y chromosome has been shrinking. Over hundreds of millions of years, it has shed about 97 percent of its original genes. Could the loss of a few more genes tip it into extinction? Not according to HHMI Investigator David Page of the Whitehead Institute for Biomedical Research. He believes that the jettisoning of genes has stopped.

In an April 24, 2014, Nature paper, Page and his colleagues compared the sequences of Y chromosomes from eight mammals, including humans, to reconstruct that chromosome’s evolution. Their results showed that, although there was a period of rapid degeneration and gene loss during the early days of its evolution, the Y chromosome retained a subset of ancestral genes that have remained