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From bite site to brain: How rabies virus hijacks and speeds up transport in nerve cells

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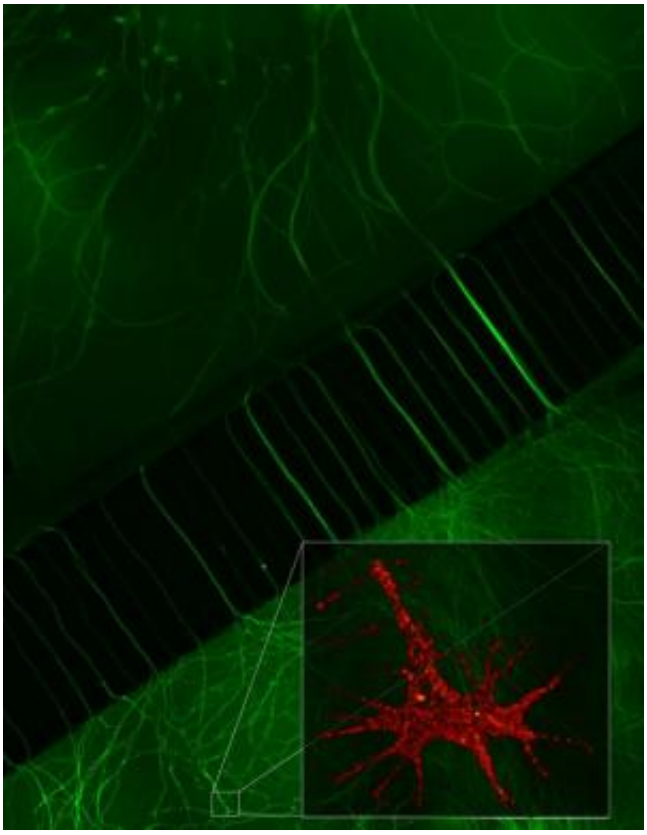

This is a dorsal root ganglia explant grown *ex vivo*. The insert shows a rabies virus (green) binding the p75 neurotrophine receptor (red) at the tip of a sensory axon. Credit: Eran Perlson and colleagues

Rabies (and rabies virus, its causative agent) is usually transmitted through the bite of an infected animal into muscle tissue of the new host.

From there, the virus travels all the way to the brain where it multiplies and causes the usually fatal disease. An article published on August 28 in *PLOS Pathogens* sheds light on how the virus hijacks the transport system in nerve cells to reach the brain with maximal speed and efficiency.

Pathogens that travel in the blood can spread throughout the body without much effort, courtesy of the heart's pumping action. Those traveling outside the blood stream and needing to cover large distances—like rabies virus which depends on the nerve cell network—need to utilize other means of transport. Nerve cells (or neurons) in the periphery, i.e. the outskirts of the body, as opposed to the central nervous system or CNS), are highly asymmetric: they have a cell body from which a long protrusion called an axon extends to another nerve cell or a target organ like muscle, along a specific transmission route. Axons can measure several hundred times the diameter of the cell body, and, in addition to rapid transmission of electric impulses, they also transport molecular materials over these distances.

Rabies virus is known to somehow use this transport system, and Eran Perlson, from Tel Aviv University, Israel, and colleagues set out to examine the details of how this occurs. The researchers set up a system to grow asymmetric nerve cells in an observation chamber and use live cell imaging to track how rabies virus particles are transported along the axons.

They focused on the p75NTR receptor, a protein which is found on the tips of peripheral neurons and known to bind a small molecule called NGF (for nerve growth factor). When NGF binds p75NTR, both are taken up into the neuron and move in acidic bubbles called "vesicles" toward the cell body. The researchers found that rabies virus behaves very similar to NGF: it binds p75NTR, both are internalized, and subsequently found in acidic vesicles that move toward the nerve cell

body.

Rabies virus is known to be able to infect neurons in the absence of p75NTR. However, when the researchers grew nerve cells that had no p75NTR in their observation chamber, they found that virus transport along the axon is less frequent and much slower. p75NTR-independent transport was also more erratic, with a larger proportion of viruses moving in the wrong direction, i.e. away from the cell body and towards the tip, suggesting that p75NTR facilitates the directed fast movement of the virus. When the researchers measured the speed of transport, they found that when rabies virus is transported with p75NTR, it moves at about 8 centimeters (a bit more than 3 inches) per day. Surprisingly, this is considerably faster (by about 40%) than the transport speed for NGF, the regular partner of p75NTR.

The authors summarize: "Our study shows that rabies virus can not only hijack the transport systems of the neuron, but might also manipulate the axonal transport machinery to facilitate its own arrival at the cell body, and from there to the central nervous system at maximum speed".

More information: *PLOS Pathogens*, dx.plos.org/10.1371/journal.ppat.1004348

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