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A billion-year arms race against viruses shaped our evolution

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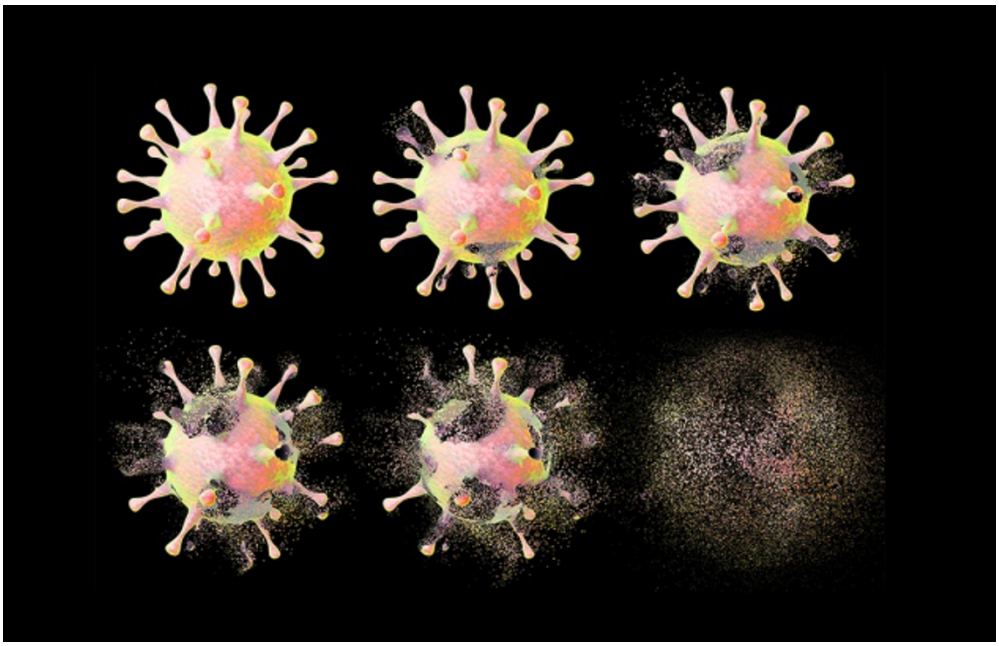
Proteins involved in gene regulation once fought viruses.



Viruses and their hosts have been at war for more than a billion years. This escalating arms race has driven a dramatic diversification of viruses and of host immune responses. Although the earliest antiviral systems have long since vanished, researchers may now have recovered remnants of it embedded like a fossil in human cells.

A protein named Drosha, which helps to control gene regulation in vertebrates, also tackles viruses, researchers report today in *Nature*[1]. They suggest that Drosha and the family of enzymes from which it descends, called RNAse III, were the original virus-fighters in a single-celled ancestor of animals and plants. "You can see the footprint of RNAse III in the defence systems through all kingdoms of life," says Benjamin tenOever, a virologist at Mount Sinai School of Medicine in New York and lead author of the paper.

Plants and invertebrates deploy RNAse III proteins in an immune response called RNA interference, or RNAi. When a virus infects a host, the proteins slice the invader's RNA into chunks that keep it from spreading. Instead of RNAi, vertebrates ward off viruses using powerful interferon proteins. In these animals, Drosha and a related protein regulate genes within the nucleus.

But in 2010, tenOever witnessed an odd phenomenon: Drosha left the nucleus of human cells whenever a virus invaded[2]. "That was weird and made us curious," tenOever says. His team found that Drosha demonstrates the same behaviour in cells from flies, fish, humans, and plants.

To test the hypothesis that Drosha can combat viruses in vertebrates, they infected cells that had been genetically engineered to lack Drosha, and found that the viruses replicated faster. Finally, the team inserted Drosha from bacteria into fish, human and plant cells. The protein appeared to stunt the replication of viruses as well, suggesting this function dates back to an ancient ancestor of all the groups. "Drosha is like the beta version of all antiviral defense systems," tenOever says.

tenOever speculates that RNAse III proteins originally helped bacteria maintain their own RNA, and they later deployed it against the genetic material of viruses. He points out the appearance of the family in immune responses throughout the tree of life. For instance, some CRISPR systems, a virus-fighting response in archaea and bacteria, include RNAse III proteins. Plants and invertebrates deploy the proteins in RNAi. And although vertebrates rely on interferons for viral control, this study shows how Drosha still comes scuttling after viruses, like a Golden Retriever dutifully returning a stick to its owner as if it were a fallen duck.

Donald Court, a geneticist at the National Cancer Institute in Frederick, Maryland, calls that finding cool, but he doesn't buy the evolutionary scenario. "RNAse III is involved in many things, in almost all domains of life," he explains. But he sees no reason to believe that one anti-viral system evolved into the next. For instance, he says the fact that a CRISPR system includes RNAse III and other CRISPR systems don't suggests that the proteins were likely acquired for use independently and not inherited.

"It's a really intriguing story, and the data are good, but you're talking about processes that happened over millennia so it's hard to know whether it's true," says Bryan Cullen, a virologist at Duke University in Durham, North Carolina. Cullen predicts the paper will prompt researchers who study RNA and infectious diseases to test teneOver's hypothesis. "The immune system has been under tremendous

pressure to evolve as viruses overcome defenses, and this paper suggests that RNAse III has played an important role in that evolution," he says. "It's like what the Red Queen said to Alice in *Through the Looking Glass*, 'you have to keep running to stay in one place'."

References

1 Aguado, L. C. et al. *Nature* http://dx.doi.org/10.1038/nature22990 (2017).

2 Shapiro, J. S. et al. *RNA* **16**, 2068–2074 (2010).