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Human RNA silences viral DNA

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Charles Q Choi
Email: cqchoi@nasw.org

RNA silencing can defend against viruses in humans, French scientists report in this week's Science. Surprisingly, say the scientists, microRNA (miRNA) appears to form the basis of this system.

"MiRNAs were thought to be involved in the regulation of endogenous genes, whereas exogenous RNAs, in particular viral RNAs, were thought to be regulated by siRNA [small interfering RNA]," lead author Charles-Henri Lecellier at the Institute of Plant Molecular Biology in Strasbourg, France, told *The Scientist*.

Prior studies have revealed that RNA interference can destroy viruses in plants and insects, but a similar role in vertebrates has not been demonstrated. Since RNA silencing can suppress endogenous retroviruses from mobilizing in plants, yeast, worms, and flies, Lecellier and colleagues reasoned that retrotransposition of mammalian exogenous viruses might also prove vulnerable. They chose as their model system the primate foamy virus type 1, a retrovirus akin to HIV.

PFV-1 accumulation in cultured human embryonic kidney cells was strongly enhanced by the expression of the P19 silencing suppressor, suggesting that a siRNA or miRNA pathway limited PFV-1 replication in human cells, because P19 specifically binds to and inactivates both.

To identify the target and means of human RNA silencing, the investigators fused viral sequences spanning the PFV-1 genome to a green fluorescent protein (GFP) - tagged reporter gene into constructs cotransfected with PFV-1 into baby hamster kidney cells. Northern and Western analysis revealed GFP levels from construct F11 were disproportionately reduced compared to F11 mRNA accumulation, which reminded researchers of miRNA translational inhibition. The DIANA-microT algorithm revealed a high probability match between the F11 sequence and the human miR-32.

Further studies demonstrated miR-32 silencing was suppressed in P19-expressing cells. Also, anti-miR-32 locked nucleic acid oligonucleotide almost doubled progeny virus production, unlike anti-miR-23, suggesting miR-32 has a direct, sequence-specific antiviral effect.

In plants and insects, all viruses targeted by RNA interference encode proteins that suppress RNA silencing. Further studies found that in PFV-1, Tas, a viral transactivator, was that protein.

In *Arabidopsis*, transgenic Tas expression strongly decreased siRNAs and led to developmental anomalies reminiscent of those elicited by suppressors interfering with miRNA functions, such as leaf elongation and serration, suggesting Tas suppresses a fundamental step conserved from plants to mammals shared between the miRNA and siRNA pathways.

Like Tas, another protein, AC2, encoded by the DNA plant viruses, geminiviruses, is a viral transactivator that can suppress RNA silencing. "We want to investigate whether transactivation and suppression are linked or completely separate," Lecellier said.

Researchers currently think each cell type harbors its own specific miRNA repertoire, Lecellier said. "This idea could partially explain some of the differences in viral permissivity observed between

specific tissues," he said, with viruses preferentially replicating in cell types where antiviral miRNAs are not expressed or are only weakly expressed.

A miRNA response could also lead to the emergence of viral quasispecies, as viruses that can rapidly introduce synonymous mutations into their genomes, such as HIV or influenza, do so to evade silencing by miRNA. "The emergence of quasispecies is important for resistance to antiviral strategies, so studying this miRNA response could be important for studying resistance," Lecellier said.

The team saw no evidence that human cells used siRNAs to disable viruses. "So it'd be interesting to investigate whether or not mammals have lost the ability to respond to viruses using siRNAs because they have a more advanced immune system than plants and flies and worms," said Phillip Zamore at the University of Massachusetts, who did not participate in this study. It was uncertain whether the miRNAs were part of a dedicated antiviral response or whether they accidentally silenced viral RNA, he said. "It'd be interesting to see whether expression of miRNAs are vastly upregulated in viral infection," he told *The Scientist.*

Future directions should involve testing any of the several hundred human microRNAs against viruses such as HIV and influenza, said Shou-Wei Ding at the University of California at Riverside, who did not participate in this study. "Also, they studied this in cell culture, and it'd be interesting to look at this at the whole animal level," Ding told *The Scientist*.

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