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HIV-1 induces RNA silencing

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HIV-1 elicits RNA silencing in human cells, but also contains a sequence that suppresses the process, researchers report in the May issue of *Immunity*.

"Nucleic acid-based immunity in mammalian cells has been found before, but to date, there has been no single report of a natural small interfering RNA [siRNA] that is triggered by HIV in human cells," coauthor Kuan-Teh Jeang of the National Institute of Allergy and Infectious Diseases in Maryland told *The Scientist*. The virus' "counter strategy" described in the paper is also unprecedented, according to Jeang.

Coauthor Yamina Bennasser and her colleagues characterized a sequence in the HIV-1 genome that encodes a rare siRNA precursor, a short hairpin RNA that is processed by the Dicer (or by a Dicer-like) ribonuclease into small siRNAs. In addition, they found that the virus prevents RNA silencing through a suppressor present in its Tat protein, which interferes with Dicer's activity.

"It's a very nicely done and a very intriguing story," said Mario Stevenson of the University of Massachusetts, who did not participate in the study. "A number of groups, including ours, have looked at the question of whether HIV encodes RNAs that can form siRNAs. Jeang's group was able to reveal that it does before anyone else."

But John Rossi of City of Hope Beckman Research Institute in Duarte, Calif., who was not involved in the research, questioned the physiological relevance of the results. "It doesn't make much sense that Dicer, a cytoplasmic enzyme, would be inhibited by Tat, which is exclusively a nuclear enzyme," Rossi told *The Scientist*. "And the 19 base-pair hairpins they describe are not substrates for Dicer." Rossi said that "dumping tons of Tat into the cells" can lead to "all sorts of nonspecific effects."

Stevenson, however, is not concerned by those questions. "We are learning of new substrates for Dicer all the time, and some groups have shown that RNA silencing can also be achieved in the nucleus, not only in the cytoplasm. The rules by which RNA interfering machinery works are continually being tweaked and modified as we understand more about the process," he said.

What did surprise Stevenson is the idea that HIV encodes siRNA and avoids being inactivated by it by encoding a suppressor. "It seems an incredible expenditure of effort," he said, but added, "viruses will not always subscribe to human logic."

Stevenson is more interested in whether shRNAs can be effectively used against HIV as a suppressor mechanism. "If Jeang's results prove to be right, then the shRNAs therapeutic approach [which expresses a HIV specific shRNA to be processed by Dicer into an antiviral form] may not be optimal."

Jeang welcomed the debate. "What is science without criticism?" he asked. "The excitement that drives me to this work, other than the fact that it comments on an aspect of nucleic acid immunology, is that the sequence that we have characterized doesn't change. It's constantly eliciting siRNAs against the virus, forcing the virus to develop a completely new mechanism. This is telling us that there is a region in the virus' genome that, because of functional constraints, cannot mutate."

According to Jeang, HIV researchers' "holy grail" is the ability to find regions in the HIV genome that cannot mutate, and the sequence that he and colleagues have characterized seems to be one such region that cannot change for functional reasons.

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