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Virus Uses Tiny RNA to Evade the Immune System

In the latest version of the hide-and-seek game between pathogens and the hosts they infect, researchers have found that a virus appears to cloak itself with a recently discovered gene silencing device to evade detection and destruction by immune cells.

The report by Howard Hughes Medical Institute (HHMI) researchers in an article published in the June 2, 2005, issue of *Nature* may be the first to show how a virus uses the gene silencing machinery for its own infectious purposes.

In people, plants, and worms, hundreds of tiny RNA molecules can silence specific genes by interfering with larger messenger RNAs (mRNAs). That interference prevents mRNAs from making proteins. Scientists do not know which genes are hushed by the microRNAs in people, but the new study bolsters growing evidence that the little molecules can play important roles not only in normal human cells but in infected cells as well.

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"A popular notion is that the whole system of generating small RNAs was designed to be a defense by cells against viruses. Our study shows that a virus can also adapt it to evade the immune response," said HHMI investigator Don Ganem, who is at University of California, San Francisco.

Ganem studies how viruses infect people and cause disease. When scientists found that RNA interference appeared to be a basic and widespread gene regulatory mechanism, "it became clear that such a fundamental pathway

could of course be pirated by a virus,” said postdoctoral fellow Adam Grundhoff, co-first author of the paper.

Thomas Tuschl, a newly selected HHMI investigator at The Rockefeller University, had already reported the existence of several microRNAs encoded by Epstein-Barr virus, although their functions were unknown. Grundhoff and co-first author Christopher Sullivan, a postdoctoral fellow in Ganem's lab, started their search for viral microRNAs with a small virus, known as SV40, in the belief that its diminutive size would make it easier to understand the functions of any microRNAs they found.

SV40 is a relatively harmless monkey virus that can cause kidney infections in its natural simian host. In rodents, however, it can cause cancer. Although the SV40 genome has been found in some human tumors, its role in human cancer has been debated. The virus is better known as a model system that has greatly contributed to major scientific advances about how genes work.

To launch their study, Grundhoff wrote a computer program to screen the SV40 genome for possible microRNA precursors. MicroRNAs are made from messenger RNA molecules with distinctive hairpin folds. The hairpin structure is diced into a microRNA segment that works with another complex to disable other messenger RNAs with complementary sequences.

Among several dozen predicted microRNAs, the top candidate turned out to be abundantly expressed in human cells infected with SV40.

Sullivan soon found the target of the plentiful SV40 microRNA. It effectively targeted the messenger RNA for a protein known as T antigen, leading to its cleavage. “SV40 may be the world's most studied virus,” Sullivan said, “and T antigen is its most studied part.”

When SV40 enters a cell, it produces T antigen, which functions to trigger viral DNA replication. Unfortunately for the virus, T antigen also serves as a target for immune (T) cells, which can destroy infected cells and prevent the virus from spreading.

Conveniently, the microRNA that targets T antigen is made late in the infectious cycle, just when T antigen is no longer essential for virus replication. Further experiments showed that cytotoxic immune cells were more likely to kill cells infected with a mutant virus that cannot make the microRNA than the normal virus. Thus, microRNA-induced reductions in T antigen expression promote escape from antiviral T cells without affecting virus growth.

“Viruses can use the host RNA inference machinery, which is often speculated to have evolved as an antiviral mechanism, to generate small RNAs that serve their own purposes—the latest chapter in the long cat-and-mouse game known to virologists as host-virus coevolution,” the

researchers conclude in their *Nature* article.