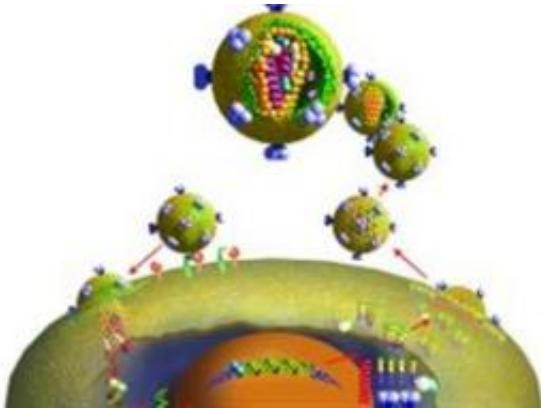


Gene Hijacked By HIV Ancestor Suggests New Way to Block Viral Reproduction

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The picture shows HIV invading a larger human cell and using human genetic machinery to make copies of the virus.

(PhysOrg.com) -- An ancestor of the AIDS virus hijacked an entire gene, perhaps from some prehistoric cat it had infected, a gene that makes it much better able to infect humans, according to a study published online today in the journal *Nature Structural and Molecular Biology*. The discovery represents the first instance in which researchers have found an entire animal gene within the genome of the human immunodeficiency virus despite 30 years of intense analyses.

Furthermore, the hijacked gene helps the virus infect humans much more efficiently, with implications for the design of new anti-HIV drugs, researchers said. Further out, studying how viruses swap genes with, and

jump between, animals may enable health authorities to anticipate and avert species jumps, like the ones made by [bird flu](#) and [swine flu](#) into humans.

“[HIV](#) molecular biology is the most studied in history, which makes it remarkable that the presence of an entire copy of this gene, called tRNA^{Lys3}, could go undiscovered within the [HIV genome](#) for decades,” said Robert Bambara, Ph.D., chair of the Department of Biochemistry and Biophysics at the University of Rochester Medical Center, and the study’s lead author. “We not only found the gene, but also a plausible explanation for why it is still there after millions of generations: its presence makes HIV dramatically better at reproducing inside of our cells. This suggests new ways to shut down with drugs the ability of the virus to mass produce copies of itself.”

Trading Genes

The current study offers the first example where an animal gene acquired by HIV helps the virus reproduce. Retroviruses like HIV are simple life forms that have evolved to stitch themselves into human [genetic machinery](#) and use it to mass produce copies of the virus. Given this mixing of genetic material, it is not surprising that retroviruses and animal cells have been swapping [genes](#) for millions of years

Faced with spacing problems in its copying process, retroviral genetic material must perform some “fancy footwork” to pass on information to the next generation of viruses. One such move is strong stop minus strand transfer, a step in the viral lifecycle discovered in 1979. To achieve the right spacing, the process breaks off one end of the viral DNA chain and transfers it to the other end. Bambara’s discovery is that such transfers are much more effective because HIV has acquired a copy of the animal gene tRNA^{Lys3}.

HIV does not start copying itself until it bumps into human [genetic machinery](#) because invading that machinery is part of its reproductive process. Specifically, past work had shown that one piece of that machinery, human tRNA^{Lys3}, kicks off strand transfer by attaching to HIV [genetic material](#) in a key spot.

In 2000, a French team found that the tRNA^{Lys3} could also attach to a second spot, a sequence nine nucleotide building blocks long, on the opposite end of the same HIV gene chain. They proposed that tRNA^{Lys3} not only initiated strand transfer, but also served as a bridge holding the two ends of the chain close together. With the chain now “curled up on itself,” it was much easier for the strong stop minus strand DNA chain to jump from one end to the other as part of HIV reproduction. Why the viral genetic code could do this was unknown.

Bambara and colleagues began searching for other sequences within the HIV genetic code that might help the original nine-nucleotide sequence link up with tRNA^{Lys3}, and increase the efficiency of minus strand transfer. The team made the “startling” discovery that the HIV gene code had come to include a full length, 82-nucleotide gene resembling the tRNA^{Lys3} gene in animals, and surrounding the original 9-nucleotide sequence. The second end of the HIV genetic code, it turned out, could link up tRNA^{Lys3} because they were each other’s mirror image.

How was it possible for the field to identify tRNA^{Lys3} as the trigger for viral replication yet not recognize for 30 years that an entire copy of the tRNA^{Lys3} gene was part of the viral genome? Ferreting meaningful patterns out of the complex HIV code is a daunting task, with some analysis made possible only through high-speed computing. For that reason, six months ago, Bambara sought out David Mathews, M.D., Ph.D., assistant professor of Biochemistry and Biophysics at the Medical Center. As computational biologists, Mathews and his team were able to combine their novel computer search program with the Bambara team’s

insights into RNA biology to reveal the gene.

In the next phase, the team will look for similarities between the tRNA-like sequences in HIV and in immunodeficiency viruses infecting cats, monkeys and lemurs. Are the viruses with this gene more virulent than those that have either lost it or evolved without it? They also hope to screen for drug candidates that block strand transfer based on their new understanding of HIV. Several pharmaceutical companies are seeking to develop such drugs as well, Bambara said.

Along with Bambara and Mathews, the work was led by Dorota Piekna-Przybylska, Ph.D. and Laura DiChiacchio within the Department of Biochemistry and Biophysics and the Center for RNA Biology at the University of Rochester School of Medicine and Dentistry. The study was sponsored by the National Institute of General Medical Sciences (NIGMS), one of the National Institutes of Health.

“This fascinating study underscores the importance of basic research in uncovering new ways to tackle disease,” said Matthew Portnoy, Ph.D., who oversees DNA replication and recombination grants at NIGMS.

“While the past 30 years of intense work on HIV have brought enormous advances in treatment, innovative research such as this will continue to push the field toward better medicines and effective vaccines.”

Provided by University of Rochester Medical Center ([news](#) : [web](#))

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