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Human Genome Bears a Virus Related to HIV-1

Buried within the genetic blueprint of every human is a snippet of DNA that resembles a gene sequence from the human immunodeficiency virus (HIV). Humans have been carrying this unwanted genetic baggage around for more than 30 million years, according to researchers from the Howard Hughes Medical Institute (HHMI) at Duke University.

"We're all walking around with a little bit of an HIV-like sequence in our genes," said Bryan Cullen, an HHMI investigator at Duke University.

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— **Bryan R. Cullen**

According to Cullen and his colleagues, an ancient family of viruses, known as HERV-K (for human endogenous retrovirus K), took up permanent residence in the genetic material of Old World monkeys shortly after they diverged from New World monkeys. The viruses then traveled with their simian and pre-human hosts as these species moved along the evolutionary path that led to *Homo sapiens*. Cullen's group published its findings in the November 9, 1999, issue of the *Proceedings of the National Academy of Sciences*.

During infection, some viruses insert their DNA into the host's genome and direct the host's cellular machinery to make the proteins needed to assemble more viruses. If this gene insertion takes place in a cell that will become an egg or a sperm, the host's offspring will have a copy of the virus in every single cell. "Once it's in there, it doesn't get out," Cullen said.

Because of these viral gene insertion events, genetic material from inactive viruses accounts for roughly 3 percent of the human genome. Cullen says that 30-50 copies of HERV-K exist in the human genome, and that some of the copies appear to be active at a low level in normal testicular and placental tissue. The HERV-K genes show even more activity in certain cancers, especially those involving the testes, "but there doesn't seem to be a harmful effect from the activity of these genes," Cullen said.

The consistent presence of HERV-Ks, however, offers insight into the evolution of both humans and viruses. First, it offers "very good evidence confirming that humans evolved from monkeys, specifically Old World monkeys." Perhaps more importantly, though, Cullen and his group determined that the HERV-K viral protein, K-Rev, functions in a manner similar to the HIV Rev protein. "This suggests that certain disease-causing tools used by HIV may have been around much longer than we had previously thought," said Cullen.

Rev, a protein which is produced by human T-cell leukemia viruses in addition to HIV, ushers viral messenger RNAs from the nucleus of a host cell into the cytoplasm, where they direct the cell's machinery to make the building blocks for more viruses. Rev accomplishes this transport by controlling a human protein known as Crm1. Without this Rev-Crm1 pair, viral messenger RNA would remain trapped inside the host's nucleus, and the virus would be unable to reproduce.

Until now, scientists had thought this activity was unique to HIV and human T-cell leukemia viruses, but Cullen and colleagues disagree. Though K-Rev appears quite different structurally from HIV's Rev, Cullen and his colleagues have demonstrated that K-Rev also hijacks Crm1 to transport mRNA from a cell's nucleus to its cytoplasm.

"The gene has been sitting in our genome all these millions of years, and it's in perfect working order," Cullen said.

Is HIV, then, descended from a virus that humans have carried for millions of years? "Probably not," Cullen said. "It's much more likely that HERV-K and HIV descended from a common ancestral virus that had Rev-like activity or that the two viruses exchanged genetic material somewhere in their evolutionary history to create Rev activity."

Cullen said that this discovery could have implications for xenografts, the untested practice of transplanting animal organs, such as kidneys, into humans. With any transplant, the recipients receive not only the organ, but also any viruses that may be living in its cells. In the case of animal-to-human transplants, the procedure brings genetic material from two different species into close contact.

"You now give these viruses an opportunity for genetic exchange, an opportunity not too different from what may have created the REV activity in the first place," explained Cullen.

But beyond such implications, Cullen believes there is a more important insight coming out of this work with K-Rev. "If we had a better idea of how viruses evolve, we might develop better strategies for countering the threats of viral infection," Cullen said.