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New Human Retrovirus Originated in Mice

Howard Hughes Medical Institute researchers and their colleagues have discovered a new retrovirus in humans that is closely related to a cancer-causing virus found in mice. Their findings describe the first documented cases of human infection with a retrovirus that is native to rodents.

The researchers discovered the virus in patients with a rare type of prostate cancer. The patients in the study have a genetic mutation that compromised some of their natural defenses against viral infection. Thus, the researchers said their discovery raises the possibility that increased susceptibility to viral infection may play a role in development of some cancers. However, they emphasized that their findings by no means implicate the virus, dubbed XMRV, in causing prostate cancer. The virus may well have flourished as a result of the failure of the defense mechanism; and other factors such as chronic inflammation may play a more direct role in the cancer.

The discovery of the new virus was made by an interdisciplinary research team led by Robert Silverman of Cleveland Clinic and HHMI investigators Joseph DeRisi and Don Ganem, both at the University of California at San Francisco. A paper describing the findings was published on March 31, 2006, in the journal, *Public Library of Science Pathogens*.

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The search for the new virus began when Silverman and his colleagues provided samples of a rare familial prostate cancer in which the viral-defense gene, *RNASEL*, had been mutated in a specific way. This mutation

compromised the function of the enzyme produced by *RNASEL*, which normally shreds viral genetic material. Infected cells carrying the shredded viral genetic material are usually targeted for destruction by the immune system. While some scientists believe that such vulnerability to viral infection is connected to prostate cancer in these rare cases, others have presented evidence contesting that theory.

To screen for viruses in the prostate tissue samples, DeRisi and Ganem used the Virochip, which was invented by DeRisi and his colleagues. The Virochip consists of a microarray of some 20,000 characteristic gene sequences -- called oligonucleotides -- representing a vast array of known viruses. The oligonucleotides are deposited as tiny spots on a small glass chip.

To detect viruses from tissue samples, the researchers isolated genetic material from each sample and tagged the genetic material with a fluorescent tracer. They then applied the fluorescently tagged genetic material to the microarray chip. Since genes tended to adhere to those with a complementary genetic sequence, any viral gene sequences in the sample would attach themselves to corresponding viral sequences on the chip. The telltale fluorescence on spots on the chip signaled the presence of viral genetic material in the sample.

Although the Virochip contains only sequences from known viruses, DeRisi said it can also detect new viruses because they invariably contain sequences that have been conserved in their evolution from related viruses.

The initial screen of the *RNASEL*-mutant prostate cancers revealed the presence of a genetic sequence that closely resembled that of a mouse virus called murine leukemia virus (MuLV). Murine leukemia virus is known as an endogenous virus because it normally exists as an integrated part of the mouse genome, rather than as independent, infective particle. MuLV is also a retrovirus, meaning its genetic material is in the form of RNA. The RNA is then reverse transcribed into DNA that is integrated into the DNA of the host cell the virus is infecting.

When the researchers isolated and sequenced the genome of the virus, they found that it was a xenotropic virus - one that can only grow in foreign cells other than mouse cells. Thus, they named the virus, Xenotropic MuLV-related virus, or XMRV.

“This finding was a big surprise because most of these endogenous viral genomes have undergone such mutation and deletion that they are incapable of giving rise to viruses any more,” said Ganem. “And while some of these viruses had been induced to grow in human cells in culture, the major question is whether such infection could ever happen in nature.

“So, one of the things that is important about our study from a virologic point of view, is that this is the first really solid example of an authentic xenotropic

retroviral infection in a human being,” said Ganem.

According to DeRisi, the Virochip made it possible to analyze these samples without preconceived biases about what viruses might be present. “Since the chip represents every known virus in one assay, it is agnostic as to what might be found,” he said. “We would never have looked for this class of virus if it wasn't for the virus chip.”

Importantly, the researchers found that prostate cancers in which both copies of the *RNASEL* gene were crippled by mutation showed much more frequent XMRV infection than did those cancers that still had one normal copy of the *RNASEL* gene.

“This link between the virus and *RNASEL* is the second finding that is important and is firmly established in this study,” noted Ganem. “We don't see the infection in people who don't have the *RNASEL* mutation, which suggests strongly *RNASEL* is an important part of the defense against retroviral infection. This is the first evidence in humans of findings that were previously made only in vitro.”

DeRisi pointed out that detailed comparison of samples of the virus between people found that - although all were XMRV - they showed tiny genetic variations. “So, while it is the same virus in each patient, the viruses are different enough to say that they are most likely independently acquired and are not the result of some contamination of the samples,” he said.

Ganem cautioned that any link between XMRV and prostate cancer is tenuous at best. “First, the genetic variant we studied occurs in familial clusters that constitute only a very small sliver of prostate cancers,” he said. “And secondly, there are many reasons to believe that the virus might not relate to prostate cancer.”

For example, he pointed out, analysis of prostate tissue by Silverman and his colleagues indicated that the virus appears only in a small percentage of connective tissue cells, called stromal cells, rather than in the tumors themselves. “So, one interpretation could be that the infection is entirely incidental to prostate cancer,” said Ganem. “The patients with *RNASEL* mutations may be more likely to get the infection or perhaps less likely to clear it. Clearly XMRV is not a classic oncogenic virus.”

Nevertheless, said Ganem, an indirect link to cancer cannot be ruled out, since “in cancer research these days, there is a lot of interest in the stroma as the soil in which cancer arises.” He added that the chronic inflammation from infection of stromal tissues may play a role in triggering such cancers.

DeRisi observed that “it may be that men who are so-called *RNASEL*-mutant are just more susceptible to viruses in general, and this susceptibility has little to do with their cancer. Nevertheless, the fact that this virus is found in tumor

tissue and that it is a new virus and the first of its kind ever documented in humans is an intriguing finding that demands to be followed up. This initial finding raises many questions. For example, what is the route of transmission? How is the virus passed from person to person? And are people the natural reservoir of this virus, or is it some other organism?"

DeRisi and Ganem said they are planning studies to explore whether XMRV is restricted to prostate cancers or whether it is more widespread in the body and in other segments of the human population. To answer such questions, the researchers are developing a blood test that can be used in epidemiological studies.