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Newly discovered virus linked to deadly skin cancer

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A new strategy to hunt for human viruses described in this week's issue of the journal *Science* by the husband-and-wife team who found the cause of Kaposi's sarcoma has revealed a previously unknown virus strongly associated with another rare but deadly skin cancer called Merkel cell carcinoma.

In the paper, University of Pittsburgh Cancer Institute (UPCI) researchers, Huichen Feng, Ph.D., Masahiro Shuda, Ph.D., Yuan Chang, M.D., and Patrick Moore, M.D., M.P.H., explain a nearly decade-long effort to harness the sequencing technology to identify the virus, which they call Merkel cell polyomavirus (MCV). While the research team emphasizes that their work does not prove MCV to be the cause of Merkel cell carcinoma, if the findings are confirmed, they may lead to new cancer treatment and prevention options.

"This is the first polyomavirus to be strongly associated with a particular type of human tumor," said Dr. Moore, professor of microbiology and molecular genetics at the University of Pittsburgh School of Medicine and leader of the molecular virology program at UPCI. "Although polyomaviruses have been studied in relation to cancer development for years, the weight of scientific evidence had been leaning toward the view that these viruses do not cause human cancers."

Polyomaviruses are a group of viruses that have been shown to cause cancers in animals for more than 50 years. But Dr. Moore noted that additional research is needed to determine what role, if any, MCV plays

in human cancer development.

A rare but extremely aggressive cancer that spreads rapidly into other tissues and organs, Merkel cell carcinoma (MCC) develops from specialized nerve cells that respond to touch or pressure. The incidence of MCC has tripled over the past 20 years to about 1,500 cases a year, especially among people whose immune systems are compromised by AIDS or transplant-related immunosuppressant drugs. About half of patients with advanced MCC live nine months or less, and some two-thirds of MCC patients die within five years.

“If these findings are confirmed, we can look at how this new virus contributes to a very bad cancer with high mortality, and, just as importantly, use it as a model to understand how cancers occur and the cell pathways that are targeted,” added Dr. Moore. “Information that we gain could possibly lead to a blood test or vaccine that improves disease management and aids in prevention.”

For example, vaccines are now available against human papillomavirus (HPV) to prevent cervical cancer, noted Dr. Chang, professor of pathology. “MCV is another model that may increase our understanding of how cancers arise, with possibly important implications for non-viral cancers like prostate or breast cancer.”

MCV has additional similarities to HPV since both viruses integrate into the tumor cell genome but not the genome of healthy cells. This integration destroys the virus’s ability to replicate normally and may be the first critical step in MCC development.

The Pittsburgh team analyzed nearly 400,000 messenger RNA genetic sequences from four samples of MCC tumor tissue using a technique refined in their lab called digital transcriptome subtraction (DTS). Comparing the sequences expressed by the tumor genome to gene

sequences mapped by the Human Genome Project, the researchers systematically subtracted known human sequences, leaving a group of genetic transcripts that might be from a foreign organism.

One sequence was similar to but distinct from all known viruses. The team went on to show that this sequence belonged to a new polyomavirus present in eight of 10 (80 percent) Merkel cell tumors they tested but only five of 59 (8 percent) control tissues from various body sites and four of 25 (16 percent) control skin tissues.

Although MCV is most commonly found in Merkel cell tumors, it also can be found in healthy people. The most important distinguishing feature is that MCV integrates into tumor cells in what is known as a monoclonal pattern, indicating that it infects the cell before the cell becomes cancerous. Tests on six of the eight MCV-positive tumors confirmed that viral DNA was integrated within the tumor genome in this monoclonal pattern, suggesting that infection with MCV could be a trigger for tumor formation. The Pittsburgh team subsequently has confirmed these results with additional tumor specimens.

Clues from elsewhere in the biomedical literature point to the existence of MCV, which has a genetic structure that is closely related to an African green monkey virus found in Germany in the 1970s. Researchers have found antibody evidence from blood tests that indicates some 15 percent to 25 percent of adults are infected with the still undiscovered human relative of this monkey virus. If MCV turns out to be this long-sought infection, then more than 1 billion people worldwide could already be infected.

“But again, look to the example of HPV,” said Dr. Moore. “Although up to 50 percent of sexually active young women are infected with HPV, a small proportion may actually get cervical cancer.”

Even if MCV is proven to play a role in MCC, Dr. Chang also cautioned that the virus is likely to be just a part of a much larger picture.

“Now we need to find out how it works,” she said. “Once the virus integrates, it could express an oncoprotein, or it could knock out a gene that suppresses tumor growth. Either way, the results are bound to be interesting.”

This is the second tumor-associated virus discovered by Drs. Moore and Chang, a husband-and-wife research team who also discovered Kaposi’s sarcoma-associated herpesvirus (KSHV) in 1993. KSHV, which causes Kaposi’s sarcoma, is the most common malignancy in AIDS patients and the most common cancer in Africa. To find KSHV, Drs. Moore and Chang used a different method to physically subtract human genetic sequences from Kaposi’s sarcoma tumors, leaving fragments of viral DNA.

Viruses, and some bacteria and parasites, are estimated to cause at least 20 percent of cancers worldwide. Over the past 40 years, few cancer-causing viruses have been confirmed in humans, including KSHV. Most of these viruses express cancer-causing proteins, called oncoproteins, in infected cells. Polyomaviruses, including MCV, possess an oncoprotein that has been shown to cause cancer after infection in animals. If MCV is confirmed to play a role in human cancer, it will be the eighth human tumor virus discovered.

Source: University of Pittsburgh