'Virus chip' detects new virus in prostate tumors

February 24 2006

UC San Francisco and Cleveland Clinic scientists have discovered a new virus in human prostate tumors. The type of virus, closely related to viruses typically found in mice, has never been detected in humans. The virus's link to human disease is still unclear, and more study is needed to determine the relationship between the virus and cancer, if any, the scientists say.

The discovery was made with the same DNA-hunting "virus chip" used to confirm the identity of the SARS virus three years ago.

While the genetics of prostate cancer are complex, one of the first genes implicated in the disease was RNASEL, a gene that serves as an important defense against viruses. Given the anti-viral role of this gene, some scientists have speculated that a virus could be involved in some types of prostate cancers in men with mutated RNASEL genes.

In the new study, the researchers discovered the novel virus far more often in human prostate tumors with two copies of the RNASEL gene mutation than in those with at least one normal copy.

"This is a virus that has never been seen in humans before," said Eric Klein, MD, a collaborator in the research and head of urologic oncology at the Glickman Urologic Institute of Cleveland Clinic. "This is consistent with previous epidemiologic and genetic research that has suggested that prostate cancer may result from chronic inflammation, perhaps as a response to infection."

"The power of the virus chip resides in its ability to simultaneously screen for all viruses, without preconceptions or bias," said Joe DeRisi, PhD, a Howard Hughes Medical Institute (HHMI) investigator at UCSF who developed the chip with colleagues in his lab. "In the case of these prostate tissues, no one would have suspected a virus of this class." DeRisi is a UCSF associate professor of biochemistry and co-leader of the study with Don Ganem, MD, also an HHMI investigator at UCSF and a professor of microbiology and immunology.

Klein reported the discovery today (February 24) at the American Society of Clinical Oncology (ASCO) prostate symposium in San Francisco. A full report of the discovery is in press in the journal PLoS Pathogens.

The new finding further validates the strategy of using the virus chip to discover previously unknown viruses and potentially uncover new viral causes for disease, the researchers say. While most other virus identification techniques require researchers to look for only a small number of candidates, the virus chip represents an unbiased search, since all known viruses are tested simultaneously.

The study is part of an on-going effort launched two years ago by DeRisi and Ganem at UCSF, using the chip, or microarray, to search for new viruses associated with a wide range of human disease. So far, the chip has been used to search for novel viruses in about 300 cases of respiratory infections and about 50 cases of meningitis, as well as a dozen or more cases of severe encephalitis, and hepatitis and leukemia.

Because the virus was probably originally acquired from another species, it is known as a xenotropic retrovirus – in this case, a xenotropic murine-like retrovirus, or XMRV. This is not the first virus of this family to be discovered, but it appears to be the first one found in humans, the scientists report.

The new virus is 96 percent identical to a class of known endogenous mouse retroviruses -- residents of the mouse genome. How the virus originally infected humans is unknown, Ganem says, though it was probably acquired from contact with rodents. It is extremely unlikely, however, that contact with mice was responsible for the virus detected in prostate tumors in the study. More likely, some form of human-to-human transmission is involved, but like many intriguing questions about the new virus's biology, the answer is not yet known, he says.

In the study, researchers examined tissue samples of 86 prostate cancer patients whose prostates had been surgically removed. Among the 20 prostate tumor samples from men with mutations in both copies of their RNASEL viral defense gene, eight of them, or 40 percent, contained the virus, while the virus was found in only one of 66 tumors from men with at least one normal copy of the gene.

The researchers don't know if the virus is unique to prostate tumors because this is the first tumor type they have studied using virus chip technology. As with most scientific discoveries, the identification of this virus in human prostate tissue prompts many more questions than it answers, they emphasize.

"A hit on the array is not the end of the project; it's the beginning," Ganem says. "Pathogen discovery is really hard work." The team intends to carry out epidemiology studies to determine how widespread the virus is, how it is transmitted, and whether it causes any of the prostate tumors, or any other disease.

The gene-hunting technique DeRisi and Ganem call the Virochip is designed to identify any virus sample by comparing its DNA or RNA to more than 20,000 snippets of genetic material derived from all known viruses -- found in humans, animals, plants, fungi and bacteria. The chip draws on computer chip technology, computation and bioinformatics,

but in essence it is a simple 3 x 1 inch glass microscope slide. Onto the slide the scientists robotically deposit 10 to 12 different DNA sequences from all known viruses.

Each sample appears as a microscopic dot, about a tenth of a millimeter in diameter –giving it the name micoroarray. Researchers then wash fluorescently tagged DNA from a sample of interest over the slide, and wherever the two sets of nucleic acid match up, they anneal to each other. The slide is then rinsed and visualized with a scanning laser microscope. The dots that have found a match glow with fluorescent light.

Source: University of California - San Francisco