HPV CANCER GENESIS

Symer, Akagi find DNA insertion loops likely spur cancer development

Human papillomavirus (HPV) causes about 610,000 cases of cancer worldwide, accounting for about 5 percent of all cancer cases and including virtually all cases of cervical cancer. Scientists have long known that certain types of HPV cause cancer, but they don't completely understand all the steps that are involved.

For example, while the HPV cancer-causing genes E6 and E7 are known to be essential for the development of cancer, they are not sufficient to cause cancer. Additional alterations in host-cell genes are necessary for cancer to develop. Recently, a team of researchers at Ohio State's Comprehensive Cancer Center identified a new way by which HPV might spark cancer development – by disrupting chromosomal DNA with repeating loops when the virus is inserted into host-cell DNA as it replicates.

"Our sequencing data showed in vivid detail that HPV can damage host-cell genes and chromosomes at the sites of viral insertion," said David Symer, M.D., Ph.D., assistant professor of Molecular Virology, Immunology and Medical Genetics at Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

Keiko Akagi, Ph.D., a bioinformatics expert and research assistant professor of Molecular Virology, Immunology and Medical Genetics at OSUCCC – James, leveraged the computational capabilities of OSC's Oakley Cluster.

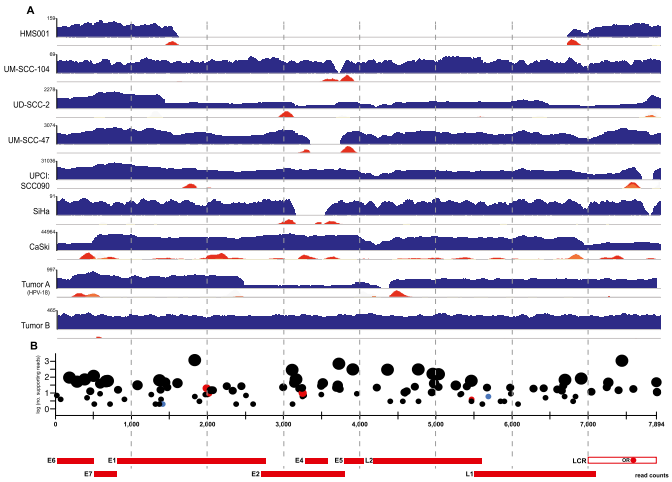
She studied whole genome sequencing data and other datasets to examine the DNA sequences of ten cancer-cell lines and two head and neck tumor samples collected from patients. Each sequence represented fragments of the roughly three billion chemical units within the human genetic instruction set.

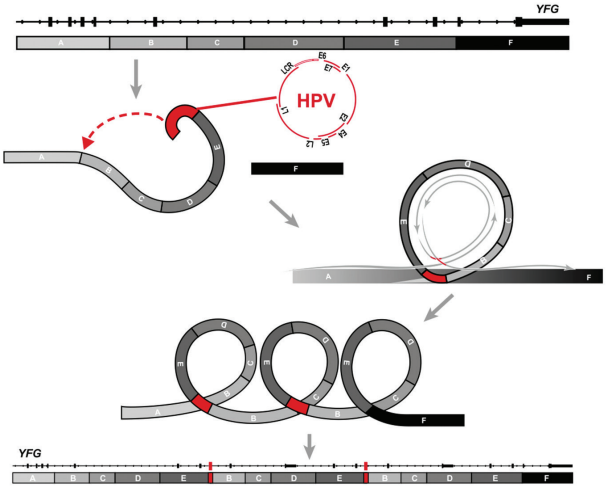
"HPV can act like a tornado hitting the genome, disrupting and rearranging nearby host-cell genes," Symer said. "This can lead to overexpression of cancer-causing genes in some cases, or it can disrupt protective tumor-suppressor genes in others. Both kinds of damage likely promote the development of cancer."

"We observed fragments of the host-cell genome to be removed, rearranged or increased in number at sites of HPV insertion into the genome," said Maura Gillison, M.D., Ph.D., professor of Medicine, Epidemiology and Otolaryngology and the Jeg Coughlin Chair of Cancer Research at OSUCCC – James. "These remarkable changes in host genes were accompanied by increases in the number of HPV copies in the host cell, thereby also increasing the expression of viral E6 and E7, the cancer-promoting genes."

Left: Histograms for various cancer samples of the HPV virome in human cancers.

Right: Focal amplifications and rearrangements explained by "looping" model.





Project Lead: David Symer, M.D., Ph.D., The Ohio State University
Research Title: Genome-wide analysis of HPV integration in human cancers reveals recurrent, focal genomic instability
Funding Source: The Ohio State University, Oral Cancer Foundation, National Institutes of Health, National Cancer Institute
Website: http://medicine.osu.edu/mvimg/directory/medical-genetics/symer-david-md-phd/Pages/index.aspx