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HPV virus helps cervical and head and neck cancers resist treatment and grow and spread

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The human papillomavirus (HPV) allows infected cervical and head and neck cancer cells to maintain internal molecular conditions that make the cancers resistant to therapy and more likely to grow and spread, resulting in a poor prognosis for patients, researchers with UCLA's Jonsson Cancer Center found.

Virtually all human cancers experience a state called intratumoral hypoxia, or a low amount of oxygen within the tumor. In the UCLA study, researchers showed that the HPV-positive cancers adapted to and took advantage of the hypoxic environment by expressing a protein that activates a cell signaling pathway that helps the cancers survive, grow and spread.

The study is published in the Nov. 4, 2008 issue of the journal *Cancer Cell*.

The research, done on cells in culture and in animal models, may lead to the development of new therapies that target the cell signaling pathway, thereby interrupting ability of the cancer cells to thrive, said Dr. Matthew Rettig, senior author of the study and a researcher at UCLA's Jonsson Comprehensive Cancer Center.

"There is potential for therapeutic intervention based on this finding," said Rettig, an associate professor of urology and medicine.

The finding is crucial because 90 to 98 percent of cervical cancers are

caused by HPV. Cervical cancer is the second most common cancer in women worldwide, with more than 500,000 cases diagnosed annually. In all, 200,000 women die from cervical cancer every year. In oral cavity and pharynx cancers, the HPV virus is linked to about 20 to 40 percent of cases, caused by sexual behavior. About 400,000 cases of head and neck cancer are diagnosed worldwide each year, and more than half of those patients die of the disease.

In those cases where the cancer is HPV-positive, which number in the hundreds of thousands, the virus will make the disease more aggressive and deadly. Finding a way to stop the virus from prompting the cancers to grow and spread more quickly could save lives, Rettig said.

"The virus appears to be regulating the expression of genes that control all of the characteristics of hypoxic tumors, those that promote survival, drug resistance and the spread of the cancers," Rettig said. "It's good for the tumor, bad for the patient."

In HPV-associated cancers, the HPV DNA is integrated into the cancer cell's genome, where it expresses a protein called E6. In the cancer cell's hypoxic environment, the protein targets a cell signaling pathway called NF-□B, heightening its activation, Rettig said. This is the first time an association has been shown between the virus and hypoxia-induced activation of the cell signaling pathway.

The findings in the study happened by coincidence, Rettig said. He and his team were screening different cancer cell types for hypoxia-induced activation of the cell signaling pathway. When he looked at the results, Rettig noted that only the cancer cell types that were HPV-positive had heightened activation of the NF-□B pathway. Cervical and head and neck cancers not caused by HPV did not have heightened activation of the pathway.

"The cells had to have the virus to have the activation," he said.

The next step for Rettig and his team is to confirm the findings in additional animal models to gain broader understanding of the potential correlation of hypoxia and activation of the cell signaling pathway in humans. He hopes to have a drug to test in human clinical studies in about five years.

HPV is the most common sexually transmitted disease in the world. About 20 million Americans currently are infected with HPV, according to the Centers for Disease Control, and another 6.2 million people become newly infected each year. At least 50 percent of sexually active men and women will acquire genital HPV infection at some point in their lives.

In addition to cervical and head and neck cancers, HPV infection has been linked to vulvar, vaginal and other female genital cancers, as well as anal, penile and other male genital cancers.

Source: University of California - Los Angeles