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Genetic breakdown in Fanconi anemia may have link to HPV-associated cancer

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A genetic malfunction that causes DNA instability in people with the blood disorder Fanconi anemia may put them at high risk for squamous cell carcinomas linked to human papillomavirus (HPV), according to a study posted online ahead of print by *Oncogene*.

Researchers led by Cincinnati Children's Hospital Medical Center report the breakdown of a cell signaling pathway for the FA (Fanconi Anemia) gene complex triggers cellular abnormalities, when then are made worse by HPV cancer genes in skin cells. This opens the door to a high risk of developing squamous cell carcinoma solid tumors, which develop from skin cells, according to the investigators.

Restoring the FA pathway reverses irregular cell growth in HPV positive cells and may reduce cancer risk, the study suggests. FA restoration also may be a potential candidate for therapy, although the researchers cautioned more research is needed before linking the findings to clinical situations.

"We are suggesting that restoring the FA pathway to treat Fanconi anemia-related cancer might be a worthwhile clinical endeavor," said Susanne Wells, Ph.D., a researcher in the division of Hematology/Oncology at Cincinnati Children's and the study's senior investigator. "This study is the first time we've been able to investigate a link between Fanconi anemia-associated cancers and HPV in cells very closely resembling living human skin, adding to the significance of this research."

Fanconi anemia is a rare, inherited genetic instability syndrome that causes aplastic anemia and an often-fatal blood disorder. This leads to bone marrow failure, organ damage and increased susceptibility to cancer. The disorder typically develops in early childhood and the average life span for people with Fanconi anemia is 20 to 30 years.

Although a bone marrow transplant can cure the blood disorder, people with Fanconi anemia remain at risk for solid tumors. The most common is squamous cell carcinoma of the head, neck, skin or anogenital region. Current treatments for these cancers are limited mainly to surgery or radiation, which is less than ideal because of underlying DNA instability in Fanconi anemia patients. The current study is part of a larger effort to find more effective and safer treatments, said Dr. Wells, also associate professor of pediatrics at the University of Cincinnati College of Medicine.

The FA gene complex and pathway are known to play an important role in DNA repair. According to this study, which used skin cells from Fanconi anemia patients, FA also helps maintain proper functioning of the cell cycle – specifically a cell's exit from the duplication of genetic material prior to division.

The current study examined Fanconi anemia-related squamous cell carcinoma with HPV because some research suggests a connection, although molecularly it remains unproven. One reason is the molecular changes that lead to cancer in FA-deficient keratinocytes (the skin cell of origin for squamous cell carcinoma) are poorly understood. This study, which uses keratinocytes, begins to help explain some of these changes.

Together with physicians in the Fanconi Anemia Comprehensive Care Center at Cincinnati Children's, Dr. Wells' team collected keratinocytes from patients. They analyzed the cells in a laboratory cell culture system

that recreates the biology of normal epithelial tissue, or skin. Fanconi Anemia patients can be deficient in one of 13 distinct genes, all working in the same pathway. Most patients have what is called the FANCA complementation group, with mutations in the FANCA gene.

The HPV cancer genes E6/E7 were artificially introduced to FANCA-patient skin cells and grown in the three-dimensional organotypic raft culture that simulates skin. The investigators observed irregular cell growth and increased skin thickness in the culture. Restoring FANCA gene function in the skin reduced irregular cell growth and skin thickness. In a reverse experiment, the researchers took FA-normal cells, where the FA gene pathway is not broken. The FA-normal cells also carried the HPV cancer genes E6/E7. The investigators then switched off two Fanconi anemia genes in the cells (FANCA and FANCD2). This disabled the FA pathway and resulted in irregular cell growth and thickening of epithelial/skin tissue.

The HPV E6/E7 genes are known to inhibit natural tumor suppression and promote chromosomal instability in the cell replication cycle. Dr. Wells and her colleagues believe FA deficiency may accelerate tumor development by promoting genomic instability, which then cooperates with HPV's inactivation of the body's natural tumor suppressors. Restoring the FA gene pathway, they suggest, can block cell cycle abnormalities stimulated by high-risk HPV E6/E7.

The researchers also experimented with standard cell cultures that aren't as close to mimicking living skin. In those experiments, cellular abnormalities did not occur until the researchers introduced DNA damaging agents, such as the chemotherapy agent mitomycin C. After exposure the cells experienced programmed death. This may explain why skin lesions develop in some Fanconi anemia patients who have residual DNA damage following certain treatments. Dr. Wells said it's also possible residual DNA damage mutates surviving cells, which can

cause cancer. The results show how sensitive FANCA-deficient skin cells are to DNA damage from external sources, highlighting in part the vulnerability Fanconi anemia patients can have to certain forms of cancer treatment.

The study's results also have potential implications for cancers not linked to Fanconi anemia. Previous research has shown inactivation of the FA pathway has been detected in some cancers affecting people without the blood disorder. The skin cell model researchers developed for the current study could be used to advance research of FA-deficient squamous cell carcinomas in the general population, they report.

Coming up next for the multi-institutional research team is trying to grow FA/HPV associated tumors in mice to see if restoration of the FANCA genetic pathway causes the cancer to shrink. Accomplishing this could lead to a preclinical model for testing novel approaches to cancer therapy, Dr. Wells said.

Source: Cincinnati Children's Hospital Medical Center

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