Researchers identify genes tied to deadliest ovarian cancers

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Scientists at the Johns Hopkins Kimmel Cancer Center have identified two genes whose mutations appear to be linked to ovarian clear cell carcinoma, one of the most aggressive forms of ovarian cancer. Clear cell carcinoma is generally resistant to standard therapy.

In an article published online in the September 8 issue of Science Express, the researchers report that they found an average of 20 mutated genes per each ovarian clear cell cancer studied. Two of the genes were more commonly mutated among the samples: ARID1A, a gene whose product normally suppresses tumors; and PPP2R1A, an oncogene that, when altered, helps turn normal cells into tumor cells. ARID1A mutations were identified in more than half of tumors studied, and, according to Siân Jones, Ph.D., research associate at the Johns Hopkins Kimmel Cancer Center, "this gene may play a significant role in this type of cancer."

The researchers say that ARID1A and PPP2R1A had not previously been linked to ovarian cancer, and "they may provide opportunities for developing new biomarkers and therapies that target those genes," says Nickolas Papadopoulos, Ph.D., an associate professor of oncology and director of Translational Genetics at the Ludwig Center for Cancer Genetics & Therapeutics at the Johns Hopkins Kimmel Cancer Center.

For the study, the scientists evaluated mutations in 18,000 protein-encoding genes in ovarian clear cell tumors from eight patients at Johns Hopkins and from institutions in Taiwan and Japan. They purified the

cancer cells, and analyzed genes from those cells and from normal cells obtained from the blood or uninvolved tissues of the same patients.

Researchers identified 268 mutations in 253 genes among the eight tumors, with an average of 20 mutations per tumor.

Next, they determined the amino acid makeup, or sequences, of four genes with the most prevalent mutations, including ARID1A, in the tumor and normal tissues of an additional 34 ovarian clear cell cancer patients. Altogether, ARID1A mutations were identified in 57 percent of the 42 tumors. PPP2R1A mutations were found in 7.1 percent of the tumors.

The landscape of cancer-related genes can be likened to a few "mountains" (highly prevalent mutations) among many "hills" (genes with less prevalence), says Papadopoulos, and "ARID1A is one of the biggest mountains found in recent years."

The protein encoded by ARID1A is a component of a cellular structure called a chromatin remodeling complex. Chromatin compresses DNA to make it fit inside cells and shields it from any other chemical signals, providing a means for controlling how and when the DNA is read. When chromatin gets remodeled, the components are shuffled and certain areas of DNA become exposed, allowing genes to be switched on or off. When the ARID1A gene is mutated, the chromatin remodeling complex is altered, allowing genes to be incorrectly switched on or off.

The Johns Hopkins scientists say mutated ARID1A can now be linked to so-called "epigenetic" changes - alterations to DNA occurring outside of the genome, in this case, the chromatin. "The mutations in ARID1A provide an important new link between genetic and epigenetic mechanisms in human cancer and may help identify epigenetic changes which can be targeted with therapies," says Victor Velculescu, M.D.,

Ph.D., associate professor of oncology at the Johns Hopkins Kimmel Cancer Center.

The researchers next plan to search for genes whose chromatin is specifically affected by ARID1A inactivation.

Ovarian clear cell carcinoma accounts for about 10 percent of cancers that start in the cells on the surface of the ovaries. It mainly affects women ages 40 to 80 and is resistant to chemotherapy.

More information: www.sciencemag.org/

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