Genetic analysis better explains how uterine cancers resist treatment

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Researchers have charted the complex molecular biology of uterine carcinosarcoma, a rare and aggressive gynecologic cancer, according to a study published on March 13 in *Cancer Cell*.

Using this new collection of genomic information, physicians will be better able to determine the specific genetic fingerprint of each patient's tumor and to find treatment options that better suit them, says lead study author Douglas A. Levine, MD, director of the division of gynecologic oncology at NYU Langone Medical Center's Perlmutter Cancer Center.

He and his colleagues found that while all uterine carcinosarcoma (UCS) tumors share some genetic traits, there is great diversity among the tumors. Instead of having a few commonly mutated genes, UCS tumors were found to have mutations (changes in DNA) in genes that play a wider variety of roles in cancer biology than previously thought.

Thus, say the authors, anti-cancer drugs, which work against specific genetic targets, are more likely to be effective against certain UCS tumors, but not against others, because there are so many different mixes of mutations. The study traced the molecular roots of UCS using genomic, epigenetic, transcriptomic and proteomic analyses to create a "new genetic atlas" for the disease.

"The biggest surprise was the genetic variety within tumors of this type," says Levine, adding that the finding helps explain why UCS has been especially difficult to treat. However, it also points doctors toward possible treatments, some already approved and others current in clinical studies.

This search for new options in urgent, adds Levine, because only about one of every three women survives longer than five years after diagnosis with uterine carcinosarcoma.

This study was conducted using tissue samples from 57 women with confirmed cases of UCS. Of the 57 women sampled, 64 percent had the cancer recur within the study follow-up period, and 58 percent died. The average follow-up period was 25.7 months.

Analysis of the 57 samples yielded 60,000 individual characteristics, which then were narrowed down to 9,149 genetic mutations. Based on this information, clinical data about UCS, and studies of other related cancers, the team identified five genes most commonly associated with UCS. One gene that normally protects against cancer, P53, was mutated in 91 percent of the tumors in the study.

In addition, UCS frequently has epithelial cells that can transition into a more harmful type of tumor-spurring, stem cell-like cancer cell, the researchers found. This trait, known as epithelial-mesenchymal transition or EMT, tends to defeat anti-cancer drugs, so newer research efforts aim to develop drugs that target EMT.

After an intensive molecular analysis of the tissue samples, the team also compared the UCS sample to data on other cancers in The Cancer Genome Atlas of the National Cancer Institute and the National Human Genome Research Institute. The Cancer Genome Atlas is a central repository of genomic data gleaned from tissue samples from more than 11,000 people, providing reference details on 33 different cancers.

According to Levine, comparing traits of UCS tumors to these large databases has revealed that UCS may be related at the molecular level to entirely different kinds of cancer. Even though that means treating UCS remains difficult, this discovery could be good news for patients and their doctors, says Levine. "Now, we can apply what we've learned to creating more specific clinical trials."

Successfully treating cancer requires interrupting the process that allows cancer cells to grow or spread to other organs. If doctors know the precise genetic mutation or mutations are involved in an individual patient's cancer, they can select chemotherapy or other treatments known to work against similar tumors.

Uterine cancers include carcinomas that originate in epithelial cells, which line or cover most organs, and sarcomas that form in muscle, fat, or bone cells, as well as in cells in tendons or ligaments. UCS has features of cancers that start in endometrial cells of the uterine lining combined with features of cancers that start in uterine muscle or connective tissues.

More information: Andrew D. Cherniack et al. Integrated Molecular Characterization of Uterine Carcinosarcoma, *Cancer Cell* (2017). DOI: 10.1016/j.ccell.2017.02.010

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