MedicalXpress

Cancer cells disguise themselves by switching off genes, new research reveals

March 30 2017

Scientists have uncovered how tumor cells in aggressive uterine cancer can switch disguises and spread so quickly to other parts of the body. In a study published in *Neoplasia*, researchers at the Washington University School of Medicine created a map showing which genes were switched on and off in different parts of the tumor, providing a "signature" of these switches throughout the genome.

The researchers say their findings support the idea that cancer cells suffer from an "identity crisis"—they switch off certain genes specific to the tissue they came from—helping them fit in more easily in different tissues, spreading the cancer. Switching these genes back on, they say, could lead to effective treatments.

Uterine carcinosarcoma is one of the deadliest forms of endometrial cancer. Unlike more common forms, it is particularly aggressive and accounts for a large proportion of the deaths related to endometrial cancer. Most tumors are made up of cells that stick to a certain growth pattern. But there can be several different types of cell in a uterine carcinosarcoma tumor, including ones that are not usually found in the uterus.

The researchers thought this ability to switch between different cell types could explain why they can spread so easily around the body; switching cell type effectively disguises the cells in different tissues. To find out how the cells change disguises, they created a map of the genes that were turned off when they were usually on, and vice versa.

"Carcinosarcoma cells show a unique ability to jump horses in mid-stream, switching from one cell type to another," said Dr. Ian Hagemann, one of the authors of the study. "It's not always changes in the DNA itself, but how the DNA is 'decorated' to turn the genes on and off—called epigenetics—that can determine cell type. I wanted to find out if there were consistent epigenetic changes in carcinosarcoma that could explain why it's so aggressive."

To determine how the cells switch from one type to another, they took three human uterine carcinosarcoma samples and sequenced the genomes of cells in two parts of each tumor: the carcinoma and sarcoma components. They analyzed the results to identify where the DNA had decorations called methylation—molecules attached that switch the gene on or off. They compared the results to healthy uterine cells.

They found that some parts of the tumor DNA had consistently more decorations and some had fewer. These epigenetic changes switched off certain genes that suppress tumors: KLF4, NDN and WT1. Understanding these epigenetic changes provides a possibility to switch the genes back on, helping the body stop the aggressive tumors from forming.

"In the past, epigenetic changes were difficult to study on a genome-wide basis," said Dr. Ting Wang, one of the authors of the study. "Our laboratory has pioneered several methods that make it possible to construct whole-genome methylation maps at single-nucleotide resolution. With these improved tools, we can now reveal epigenetic changes in cancers, which may well be just as significant as genetic mutations."

More information: Jing Li et al, Whole-Genome DNA Methylation Profiling Identifies Epigenetic Signatures of Uterine Carcinosarcoma, *Neoplasia* (2017). DOI: 10.1016/j.neo.2016.12.009

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