Ovarian cancer advances when genes are silenced

13 December 2010

There are many mechanisms that alter the activity of genes - direct changes to the DNA code like mutations and deletions, or changes that control when genes are switched on and off, called epigenetic means. Tumor-suppressor genes are often inactivated through epigenetics, which provides an opening for the cancerous growth of cells.

Researchers at the Duke Cancer Institute have found evidence of epigenetics at work on a genome-wide scale in cases of ovarian cancer. One major biological signaling pathway in particular was found to contain many genes influenced by DNA methylation - a mechanism for turning off genes -- in tumor cells.

The researchers performed a series of studies on cancer cell lines and primary tumor specimens from ovarian cancer patients by comparing the genome-wide gene expression profiles of cells that were treated or mock-treated with drugs that inhibit DNA methylation. From these studies they identified 378 candidate methylated genes. From this group, all 43 of the predicted genes the researchers analyzed showed methylation in ovarian cancers.

"We were very surprised to see that so many of these genes were part of one pathway, the TGF-beta signaling pathway, so we conducted studies to further explore how methylation might have an effect on the pathway," said senior author Susan Murphy, Ph.D., assistant professor in the Division of Gynecologic Oncology in Duke OB-GYN and in the Department of Pathology.

When the researchers treated tumor cells with methylation inhibitors, the TGF-beta pathway showed increased activity. This is an important signaling pathway that directs many processes in cells. A smoothly functioning TGF-beta pathway ensures proper cell growth, cell differentiation, and apoptosis (programmed cell death), and helps prevent tumor formation. When this pathway is deregulated, it can instead help tumors grow and metastasize.

The study showed for the first time that TGF-beta pathway function is regulated through methylation. "This is only one piece of a larger puzzle about the biology of ovarian cancer, but we can say that DNA methylation does have an influence on suppressing TGF-beta pathway signaling, which contributes to ovarian cancer."

In addition, the genes they studied included a cluster of genes that strongly correlated with TGF-beta pathway activity in specimens from older women, which suggested that age-related epigenetic changes can accumulate and may contribute to cancer.

Murphy said two different groups of patients the team identified might need different approaches.

"Some women with ovarian cancer have lower expression of these tumor-suppressing genes and may be amenable to epigenetic therapies that lead to gene reactivation - with the caveat that at this point we can't epigenetically reactivate just one gene or a specific group of genes," Murphy said. "Another group of women with ovarian cancer have higher expression of these genes, suggesting it may be possible to specifically inhibit particular components in this pathway to stop tumor development or progression."

More information: Matsumura N, Huang Z, Mori S, Baba T, Fujii S, Konishi I, Iversen ES, Berchuck A, Murphy SK. Epigenetic suppression of the TGF-beta pathway revealed by transcriptome profiling in ovarian cancer. *Genome Res* doi:10.1101/gr.108803.110

Provided by Duke University Medical Center