Genes behind aggressive endometrial cancer found

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In a major breakthrough for uterine serous carcinoma (USC)—a chemo-resistant, aggressive form of endometrial cancer, Yale researchers have defined the genetic landscape of USC tumors, findings that point to new treatment opportunities.

The collaborative team—which included researchers with expertise in gynecological cancer, genomics, and computational biology— identified a number of new genes that are frequently mutated in USC. The results of this comprehensive genetic analysis of USC are published in the Jan. 28 Proceedings of the National Academy of Sciences (PNAS) online early edition. The researchers were supported as part of a collaborative program with Gilead Sciences, Inc.

Endometrial cancer is the most prevalent gynecologic tumor in women, with over 47,000 newly diagnosed cases and about 8,000 deaths in 2012 in the United States alone. Patients with type I endometrial cancer tumors generally have a good outcome, but those with type II, or USC, have more relapses and deaths, and the disease is more aggressive.

"We have clearly identified the mutations that are responsible for USC tumors," said senior author of the study Alessandro Santin, M.D., professor of obstetrics, gynecology and reproductive sciences at Yale School of Medicine, and program leader of the gynecological cancers program at Smilow Cancer Hospital at Yale-New Haven and a member of Yale Cancer Center. "In addition to a number of well-known cancer genes, we found three genes that had not previously been associated with

cancer that are found in these tumors. This finding points to new pathways that could be important in developing therapies down the road."

The team collected tumors from 57 women affected with USC to try to determine the molecular basis of the tumor's aggressive behavior. They sequenced all the genes from the tumors and identified mutations that are crucial for these tumors to grow. The team also studied the copy number variations—genes that are not mutated but are amplified in the tumors to give them a growth advantage over normal tissues.

The newly-identified cancer-related genes included two—CHD4 and MBD3—that are found in the same protein complex and play a role in remodeling the genome to allow certain regions to be turned on and off. The discovery of a third gene, TAF1, was a surprise to researchers because it is a core component of the machinery responsible for transcribing a large fraction of the protein coding genes in the human genome.

"The detailed study of different cancers continues to produce new and unexpected discoveries," said corresponding author Richard P. Lifton, M.D., Sterling Professor, chair of genetics at Yale, and a Howard Hughes Medical Institute investigator. "These new findings define the biological basis of this cancer, and suggest new opportunities for personalized therapy."

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