Study pries into ovarian cancer's deadly secrets

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A new University of Michigan Medical School study sheds light on cell defects that lead to one common type of ovarian cancer and puts forth a promising new mouse model that already is being used for preclinical drug testing.

The study, published in the April issue of *Cancer Cell*, focuses on ovarian endometrioid adenocarcinoma, the second most common form of a baffling, deadly disease for which early detection methods and effective treatments have been elusive so far. The American Cancer Society estimates there will be 22,430 new cases of ovarian cancer and 15,280 deaths from the disease in the United States this year.

The new mouse model developed in the U-M lab is based on molecular defects shown to be present in human ovarian tumor cells, says senior author Kathleen R. Cho, who treats patients as a member of the U-M Comprehensive Cancer Center. Cho's and others' existing mouse models, if designed to mimic the four major types of ovarian cancer, should provide key tools for learning how gene mutations and cell changes lead to disease, and for finding treatments during ovarian cancer's early stages, when treatments are most likely to be effective.

"We need models to do preclinical testing of new drugs that target the specific molecular defects in a patient's tumor cells," says Cho, a professor of pathology and internal medicine at the U-M Medical School. Using the genetically engineered mice her lab developed, one preclinical study is already under way, testing an existing drug called

Rapamycin. The lab's mouse model can also be used to test new drug candidates that inhibit the cell-messaging systems defective in ovarian endometrioid adenocarcinoma.

Cho says possible new treatments taking advantage of the lab's findings are probably several years away.

In the new paper, Cho, lead authors Rong Wu and Neali Hendrix-Lucas, and other members of Cho's team report that defects in two cellular signaling pathways occur together in a subset of ovarian endometrioid adenocarcinomas and appear to cooperate in the development of human tumor cells. They examine the effects of altered genes in the Wnt/â-catenin and PI3K/Pten signaling pathways, each implicated in several types of cancer.

Genes that are mutated in ovarian cancer, as in other cancers, result in the production of proteins that alter the normal function of signaling pathways in cells. Defects in these pathways can prevent the normal action of tumor suppressor genes and allow cancer to develop and grow.

The researchers analyzed gene mutations and signaling pathway defects in human ovarian tumor cells, then created a strain of genetically engineered mice with the same defects to see if ovarian tumors would develop. In all of the mice altered to possess both pathway defects, ovarian tumors — similar in morphology and biological behavior to human ovarian endometrioid adenocarcinomas — rapidly developed and often metastasized.

To create the new mouse model for ovarian endometrioid adenocarcinoma, Cho's research team used two existing types of transgenic mice to breed mice that expressed the two signaling defects they wanted to study.

"Among other things, the study has the potential to improve our understanding of early ovarian cancer," Cho says. "In the last 30 years, we haven't done a lot to improve the overall survival of ovarian cancer patients."

Women and their doctors at present have no effective ways to detect ovarian cancer at an early, treatable stage. There are few if any early physical symptoms of ovarian cancer and no tests to detect cellular changes that might indicate precancerous lesions, as Pap smears do for cervical cancer. By the time a woman with ovarian cancer experiences symptoms, tumors are typically large and often metastatic.

Standard therapy for ovarian cancer now usually involves surgery to remove the tumor, followed by chemotherapy, which is initially effective but not curative. The disease frequently comes back in a drug-resistant form. New drugs are badly needed that can target the distinct molecular defects in the different types of ovarian cancer, which may be more accurately seen as not one disease, but several related ones.

Next, Cho plans to tackle the "very big challenge" of dissecting the molecular basis of serous ovarian cancer, the most common form of ovarian cancer and the one responsible for most ovarian cancer deaths.

That work, combined with ongoing projects on ovarian endometrioid adenocarcinoma, could help researchers develop screening tests that can detect the most common types of ovarian cancer early, and design more effective treatments for women with advanced disease.

Source: University of Michigan