Study reveals why certain ovarian cancers develop resistance to platinum-based chemotherapy

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A team of researchers led by Fred Hutchinson Cancer Research Center has identified a new mechanism that explains why some recurrent ovarian tumors become resistant to treatment with commonly used platinum-based chemotherapy drugs such as cisplatin and carboplatin. They describe their research online Feb. 10 in the journal *Nature*.

While these findings are based on the study of ovarian-cancer cells from women with inherited mutations in the BRCA2 gene, they also may help explain the mechanics of cisplatin resistance in ovarian-cancer patients with BRCA1-gene mutations. Together such genetic mistakes are thought to cause about 10 percent of ovarian cancers, according to senior author Toshiyasu (Toshi) Taniguchi, M.D., Ph.D.

“Because BRCA1 and BRCA2 have similar functions in terms of DNA repair, we may be able to generalize these findings for women with either mutation,” said Taniguchi, an assistant member of the Hutchinson Center’s Human Biology and Public Health Sciences divisions.

BRCA2 works to repair damaged DNA; inherited mutations in this gene disrupt that ability, which increases the risk of ovarian and breast cancer. At the same time, such mutations also make cancer cells more vulnerable to DNA-damaging agents such as cisplatin and carboplatin. While ovarian tumors initially respond very well to platinum-based chemotherapy, eventually between 70 percent and 80 percent of

advanced-stage ovarian-cancer patients develop a resistance to these drugs.

“The majority of advanced-stage ovarian-cancer patients die due to acquired resistance to platinum-based drugs. It is a serious problem,” he said.

Taniguchi and colleagues at the Hutchinson Center, University of Washington, Cedars-Sinai Medical Center and the Mayo Clinic have uncovered how such resistance occurs. They found that when exposed to cisplatin, some ovarian-cancer cells develop secondary mutations on their BRCA2 gene that restore the gene’s ability to repair DNA. This restoration of gene function then makes the cancer cells resistant to chemotherapy.

“This event is unlike any previous mechanism of resistance to chemotherapy identified in cancers,” said co-author Elizabeth Swisher, M.D., associate professor of medicine in the Department of Obstetrics and Gynecology and director of the Breast and Ovarian Cancer Prevention Program at the University of Washington. “By identifying the cause of chemotherapy resistance in these cancers, we may be able to better predict who will respond to different chemotherapy agents and find novel ways to re-sensitize tumors to chemotherapy that otherwise would not have had a good response to treatment.”

If women with recurrent ovarian cancer are found to have a secondary mutation on their BRCA2 gene, their cancer likely would be resistant not only to platinum-based compounds but also other drugs such as PARP inhibitors. “Testing whether relapsed tumors have a secondary mutation of BRCA2 may be important to predict clinical outcome,” Taniguchi said.

The researchers suspect they may be able to generalize their findings

regarding secondary mutations in BRCA2 to other DNA-repair genes, such as BRCA1, which may help explain drug resistance to a variety of cancers, including those of the breast, prostate and pancreas.

Source: Fred Hutchinson Cancer Research Center