Researchers find possible key to preventing chemotherapy resistance in ovarian cancer

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For patients with ovarian cancer and their physicians, resistance to chemotherapy is a serious concern. However, researchers at Moffitt Cancer Center have identified a molecular pathway that may play a key role in the evolution of chemotherapy resistance. They are hopeful that the discovery may lead to therapies that are tailored to individual patients with ovarian cancer; reversing resistance to chemotherapy and improving survival from the disease.

"Few clinical or biologic events affect survival for patients with ovarian cancer more than the way their tumors respond to chemotherapy," said Johnathan Lancaster, M.D., Ph.D., senior author on a study into chemotherapy resistance recently published in the journal Clinical Cancer Research (17:00, 2011). "We identified a pathway called the 'BCL2 antagonist of cell death,' or BAD, and determined that the activity of the BAD pathway may have more influence on survival than the volume of residual disease after primary surgery."

According to Lancaster and colleagues, the discovery of BAD opens the door to using the pathway as a biomarker to identify patients with the highest-risk ovarian cancer, which are genetically programmed to be resistant to chemotherapy; enabling physicians to identify patients who might benefit from drugs that inhibit the BAD pathway such that chemo-resistance is reversed.

"Targeted therapies that increase a tumor's sensitivity to chemotherapy offer the potential to improve patient survival," explained Lancaster,

chair of the Department of Women's Oncology and director of the Center for Women's Oncology at Moffitt.

By treating ovarian cancer cells in a test tube (in vitro) with a chemotherapy drug and observing which genetic pathways became most active, the researchers identified the BAD pathway. To further analyze the activity of the BAD pathway and levels of the BAD protein, the researchers examined tumor specimens and genomic information from almost 300 patients with advanced ovarian cancer. A 47-gene BAD pathway signature was developed and was found to be associated with survival. Subsequent in vitro tests on ovarian cancer cells suggest that it may be possible to inhibit the BAD pathway and reverse resistance to chemotherapy.

"Intriguingly, patients who had lots of cancer remaining at the conclusion of their surgery but whose tumors had low levels of pBAD protein, had better survival than patients with very little cancer remaining following surgery, but who had high levels of pBAD protein," said Lancaster. "Although our data highlights the importance of this newly identified pathway, not all cell line samples showed associations between chemotherapy resistance and BAD pathway genes. There are likely many other pathways and processes contributing to chemotherapy resistance."

The researchers concluded that although more research is necessary, BAD pathway-based biomarkers could open the door to personalized treatment for ovarian cancer by placing women in high-risk and low-risk groups based on their genetic profile for the BAD pathway and protein. Treatments could be selected for each patient according to the status of their BAD pathway.

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