Study finds relationship between PTEN loss, potential for immune response in BRCA 1/2-deficient ovarian cancer

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The protein known as phosphatase and tensin homolog (PTEN) is frequently mutated or affected by cancer as tumors develop. Now a new study from the Basser Center for BRCA at the Abramson Cancer Center of the University of Pennsylvania shows PTEN may serve as a marker for whether a patient with BRCA 1-2 deficient ovarian cancer is likely to respond to checkpoint inhibitor therapy. Researchers found the tumors that had PTEN loss were less likely to generate an immune response than tumors that maintain PTEN levels. They will present their findings at the American Association for Cancer Research Annual Meeting in Chicago on Wednesday (Presentation #5729).

BRCA1/2-deficient ovarian cancer is a specific subset of ovarian cancer. Genes known as BRCA1 and BRCA2 are involved in cell growth and the repair of damage to DNA. Mutations or deficiencies in these genes can cause DNA to go unrepaired, which increases the chance of developing cancer. These cancers are often initially susceptible to treatments that damage the tumor's DNA, such as platinum chemotherapy, but most develop resistance and require other treatment strategies. One strategy is the use of anti-PD1/PDL1 immunotherapies. Although clinical trials have collectively shown a disease control rate of approximately 45 percent using this approach in ovarian cancer, they have yet to establish selective benefit in BRCA1/2-deficient cancers, which should generate stronger anti-tumor immune responses given their higher mutation rate.

Researchers in the Basser Center for BRCA analyzed data on 86 ovarian tumors, from the Cancer Genome Atlas (TCGA—68) as well as from Penn (18), to evaluate potential immunosuppressive mechanisms in BRCA1/2 deficient tumors and to identify factors that may determine response to PD1/PDL1 inhibitors.

"PTEN is a genomic marker we already routinely measure, and based on published data we wanted to know if we could use it to predict which BRCA1/2 mutated tumors are likely to respond to checkpoint inhibitors and which are not," said the study's senior author Katherine L. Nathanson, MD, deputy director of the Abramson Cancer Center and director of Genetics at the Basser Center for BRCA. Adam Kraya, Ph.D., a post-doctoral fellow at Penn, was the study's lead author and will present the findings at AACR.

The TCGA analysis showed tumors with PTEN loss in the background of BRCA1/2 deficiency had lower levels of cytolytic immune molecules and immune-activating pathways that would normally drive immune responses against tumors. In Penn ovarian tumors, the levels of immune molecules like CD3, CD8, FoxP3, and PRF1 were found at significantly lower levels with PTEN loss. These data suggest that immune cells were not able to infiltrate tumors as effectively nor mount anti-tumor responses when PTEN is lost. In other words, PTEN loss correlates with loss of molecules that can generate an immune response.

"This is an effect we've seen in other disease types like melanoma and leiomyosarcoma, but this is the first study to identify the effect in BRCA-deficient ovarian cancer," Nathanson said.

Nathanson and her team are also investigating a similar question in breast cancer.

Provided by Perelman School of Medicine at the University of Pennsylvania