SWOG cancer research network study opens window into immune microenviroment

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The first comprehensive study of immune cell types in pre- and post-chemotherapy cancer tissues points up a host of targets for new or existing cancer drugs that could improve patients' sensitivity to both chemotherapy and immunotherapy.

Results from the SWOG Cancer Research Network study appear in the latest issue of the *Journal for ImmunoTherapy of Cancer*. The results provide a detailed look at the immune cells found in breast cancer tumors before and after chemotherapy—providing scientists a rare window into the immune microenviroment and how it's affected by cancer drugs.

"When we better understand the types and functions of immune cells found in cancer tissue, and the effects of drugs on those cells, the closer we get to finding effective treatments," said Lajos Pusztai, MD, chair of SWOG's breast cancer committee and senior author of the journal article. "With this study, we get a unique look at the tumor immune microenvironment—and identify potential therapeutic targets that can be tested in the clinic."

SWOG is a publicly funded cancer research network that has run over 1,400 National Cancer Institute funded trials since 1956. A major benefit of that longevity: the accumulation of over 800,000 blood, tissue, and other specimens in SWOG's biobank. Pusztai, of Yale Cancer Center, and his SWOG team located 60 paired tissue samples in the bank that were taken for S0800, a randomized trial that compared two pre-

surgical chemotherapy treatments for patients with HER2-negative, locally advanced, or inflammatory breast cancers.

The team used this subset of paired pre- and post-treatment tissues to accomplish three goals: determine the presence of the cancer-attacking immune cells known as tumor infiltrating lymphocytes (TILs); measure the expression of the immune-suppressing protein PD-L1, and the expression of 750 other immune-related genes that can show immune cell activity in pre- and post-treatment tissues.

To do this work, Pusztai and his team used three methods. These included a pathologist counting TILs under a microscope, and laboratory scientists using an assay to determine PD-L1 expression. In addition, article lead author Xiaotong Li, a computational biologist at Yale, used another assay, the NanoString PanCancer IO 360 Gene Expression Panel, to measure the expression of 750 immune-related genes with the help of a team of from NanoString.

Here are the results:

- The team found higher counts of cancer-fighting TILs in the pre-treatment tissue samples of breast cancer patients who saw their cancer disappear after chemotherapy, a phenomenon known as pathologic complete response, or pCR. The TIL counts in post-treatment tissues were significantly lower when compared with pre-treatment tissues, suggesting that immune cells are killed by chemotherapy agents.
- Researchers did not find any significant changes to PD-L1 protein expression in any of the comparison groups—between patients whose tumors disappeared to those whose tumors merely shrunk, or between pre- and post-treatment tissue samples.
- The team found 24 immune genes more highly expressed in patients who saw a complete response to chemotherapy,

including genes that control the cell-killing enzymes granzyme and granulysin and the cytokines CCL21 and CCL19, proteins that activate cancer-fighting T cells. The IL7R gene that controls the production of T calls is also more active in patients who saw their cancer disappear after chemotherapy. This suggests that these molecules play an important role in activating and attracting immune cells—and any drugs that increase their expression or activity could improve treatment response.

- The team found that the proteins CXCL1, CXCL2, CXCL3, and CCL20, and the IL6 gene, were more highly expressed in patients who did not get a complete response to chemotherapy. This suggests that drugs that decrease the presence of these proteins and the activity of this gene could improve treatment response.

"Our findings revealed several highly actionable immune targets that can get tested in the clinic," Pusztai said. And, in fact, he is already doing so. Pusztai is leading S1418, a SWOG breast cancer trial testing the immunotherapy drug pembrolizumab, which targets PD-1, to find out if it will improve survival of triple negative breast cancer patients who have PD-L1 expression in their cancer after pre-operative chemotherapy.

Provided by SWOG