Study identifies genes linked to resistance to breast cancer chemotherapy

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A study led by Vanderbilt-Ingram Cancer Center (VICC) investigators has identified a gene expression pattern that may explain why chemotherapy prior to surgery isn't effective against some tumors and suggests new therapy options for patients with specific subtypes of breast cancer.

The study by lead author Justin Balko, Pharm.D., Ph.D., was published online June 10, 2012 in *Nature Medicine* in advance of print publication. Balko is a postdoctoral fellow in the laboratory of Carlos L. Arteaga, M.D., associate director for Clinical Research and director of the Breast Cancer Program at VICC, who led the study.

About 30 percent of breast cancer patients have a pathological complete response when chemotherapy is used to shrink tumors prior to surgery. However, many patients still have residual cancer in the breast after neoadjuvant chemotherapy (NAC) is completed. These patients are at a higher risk of cancer recurrence and death.

The investigators suspected that profiling tumors after neoadjuvant chemotherapy would identify genes associated with resistance to this form of treatment. They studied gene expression patterns in 49 breast tumors obtained during surgery after four months of NAC.

They identified and analyzed specific groups of genes associated with high-grade, chemotherapy-resistant tumors, labeling their 244 unique genes the CLUSTER signature, and combined this panel with previously identified gene signatures to search for distinctive patterns of behavior.

The investigators found that low concentrations of dual specificity protein phosphatase 4 (DUSP4) is strongly correlated with faster tumor cell growth following neoadjuvant chemotherapy. Low DUSP4 was also correlated with a type of breast cancer known as basal-like breast cancer (BLBC). DUSP4 promoter methylation and gene expression patterns of Ras-ERK pathway activation were also higher in BLBC relative to other breast cancer subtypes.

When DUSP4 was present, chemotherapy was effective against cancer cells, whereas when DUSP4 was experimentally deleted, there was a much lower response to chemotherapy.

"These data suggest that cells with low DUSP4 expression are enriched during NAC and that low DUSP4 expression in residual resected breast tumors is a potential biomarker for drug resistance and a high likelihood of tumor recurrence," said Balko.

The group also hypothesized that DUSP4 may be a potential biomarker for response to drugs that inhibit the MEK kinase. Using DUSP4-deficient tumors established in mice, they compared treatment with the chemotherapy drug docetaxel, with and without the MEK inhibitor selumetinib. This study showed that the combination was much more effective than docetaxel alone at eliminating the mouse tumors.

"These data support exploratory clinical trials combining chemotherapy and MEK inhibitors in patients with DUSP-deficient basal-like breast cancer," said Balko.

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