Protein protects against breast cancer recurrence in animal model

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According to the American Cancer Society, nearly 40,000 women in the United States will succumb to breast cancer this year. Most of these women will die not from the primary tumor but rather tumor recurrence – the reappearance of the disease following treatment.

Precisely what causes breast cancer recurrence has been poorly understood. But now a piece of the puzzle has fallen into place: Researchers at the Perelman School of Medicine, University of Pennsylvania have identified a key molecular player in recurrent breast cancer – a finding that suggests potential new therapeutic strategies.

The study, performed in the laboratory of Lewis A. Chodosh MD, PhD, chair of Cancer Biology and director of Cancer Genetics at the Abramson Family Cancer Research Institute, implicates the tumor suppressor protein Par-4 in recurrent breast cancer.

Par-4 is downregulated in recurrent tumors, and knocking the gene's expression down accelerates tumor recurrence in a mouse model of recurrent breast cancer. Conversely, overexpressing Par-4 delays the onset of tumor recurrence.

Data from human breast cancer patients confirm these findings. The authors analyzed patient tumors from the I-SPY 1 TRIAL, a clinical trial that measured tumor gene expression patterns and response to neoadjuvant chemotherapy. They found that Par-4 expression is low in "residual disease" (that portion of a tumor that survives chemotherapy)

compared to the primary tumor prior to treatment, and that women with low Par-4 levels in their primary tumors tend to respond less well to treatment and are more likely to experience a relapse.

The findings appear in this week's issue of *Cancer Cell*.

The study was led by Chodosh senior postdoctoral fellow, James V. Alvarez, PhD. Alvarez and his colleagues teased apart the role of Par-4 using a mouse model of recurrent breast cancer. In this model, turning "on" the HER2/neu oncogene in mice—which is turned on in about 20% of human breast cancers—induces the formation of a primary mammary tumor. Subsequently, turning HER2/neu "off" in a tumor that has arisen causes it to essentially disappear, mimicking the treatment of primary human breast cancers with the anti-HER2/neu agent, Herceptin. But, as in many human patients, at some point in the weeks and months following tumor regression, tumors often return, both in the breast as well as in secondary sites such as the lungs.

By studying these paired primary and recurrent tumors, Alvarez, Chodosh, and their colleagues found that Par-4 expression was dialed down in recurrent tumors relative to primary tumors. When they examined gene expression data from human breast cancer specimens, they found that low Par-4 expression was associated with an increased risk of recurrence and a poorer response to neoadjuvant therapy—chemotherapy prior to surgery. A poor response to neoadjuvant therapy is associated with an increased likelihood of recurrence.

Based on these findings, the team hypothesized that cells that downregulate Par-4 may be more adept at surviving chemotherapeutic treatment of the primary tumor, and that's precisely what they found. When they compared cells expressing normal levels of Par-4 with cells that had downregulated the gene, they found that it is the cells with low

Par-4 levels that persist following treatment. Consequently, it is these cells that are available to give rise to recurrent tumors in the future.

The team then asked what Par-4 actually does to prevent breast cancer recurrence. They found in their mouse models that when HER2/neu is turned off and primary tumors shrink, Par-4 expression ramps up. This causes a defect in cell division, producing cells with more than one nucleus. This, in turn, leads to cell death. Cells that have downregulated Par-4 fail are able to escape this multinucleation process, allowing them to survive therapy and, eventually, give rise to a recurrent tumor.

The bottom line, Alvarez says, is that Par-4 downregulation is both a necessary and sufficient step for breast tumor recurrence. "Par-4 downregulation allows tumor cells to survive tumor regression caused by oncogene inhibition or chemotherapy."

That conclusion suggests that strategies that increase Par-4 expression in tumors could pay therapeutic dividends. In fact, turning Par-4 back on in recurrent tumor cells led to their rapid death. However, "drugging' Par-4 won't be easy", he says.

Par-4 is a tumor suppressor protein that functions through interactions with other proteins. Neither an enzyme nor a signaling receptor, it is not a traditionally "druggable" molecule. However, if researchers can identify the biochemical pathway that controls Par-4, or molecules that can modulate Par-4 activity directly, they may be able to increase the efficacy of neoadjuvant therapy of primary tumors as well as treat recurrent breast cancers more effectively, Alvarez says. The team is now working on identifying pathways that regulate Par-4 levels.

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