

## VIEWPOINT

# Par-4 prevents breast cancer recurrence

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### Abstract

Therapy resistance and disease recurrence are two of the most challenging aspects in breast cancer treatment. A recent article in *Cancer Cell* makes a significant contribution toward a better understanding of this therapeutic problem by establishing downregulation of the tumor suppressor Par-4 as the primary determinant of breast cancer recurrence. This viewpoint brings forth the importance of their findings and its implications on future research and therapy.

### Background

The primary hurdle in breast cancer therapy is the treatment of tumors which are hormone receptor-negative or triple-negative breast cancers. These tumors tend to be highly resistant to chemotherapy and targeted therapies alike and exhibit a high propensity for recurrence. Once the cancer recurs, the average survival is less than 12 months [1]. Breast cancer is the most commonly diagnosed cancer among women and is second only to lung cancer in terms of cancer deaths [2]. Despite advances in breast cancer research and therapy, over 40,000 deaths in 2013 alone are expected in the US [3].

Breast cancer is characterized by its hormone receptor status that also determines the treatment options that are currently available. Surgery and neoadjuvant chemotherapy have been the mainstay for breast cancer management for a number of years. However, the advent of targeted therapies in combination with chemotherapy has resulted in improved pathological complete response [4]. Currently, a number of targeted therapies such as trastuzumab, pertuzumab, or tamoxifen are designed to kill tumors that are hormone receptor-positive [5]. As a result, patients presenting with positive status for estrogen receptor, progesterone receptor, and/or human epidermal growth factor receptor 2 respond

well to these targeted regimens, showing increased remission and prolonged disease-free survival.

A recent article by Alvarez and colleagues [6] identifies loss of Par-4 as the fundamental factor leading to breast cancer recurrence. Par-4 is a tumor suppressor that is unique in its ability to selectively induce apoptosis in cancer cells but not in normal cells [7].

### The article

The study by Alvarez and colleagues [6] describes pre-existing heterogeneity in a primary tumor population with respect to Par-4 expression and presents a convincing two-step model for breast cancer recurrence in oncogene-addicted cells. Apoptotic stimuli such as oncogene inhibition or treatment with chemotherapeutic agents cause an acute upregulation in the expression of Par-4 in these tumor cells, leading to Par-4-induced ZIP-kinase-dependent MLC2 phosphorylation, multinucleation, and ultimately apoptosis due to cytokinesis failure. This leads to the initial tumor regression observed with oncogene inhibition or chemotherapy. This study therefore unravels a novel mechanism for Par-4-induced apoptosis in oncogene-dependent tumor cells. Pre-existing tumor cells expressing inherently low levels of Par-4 fail to elicit this response, which enables them to survive such apoptotic insults. These cells, therefore, constitute the residual subpopulation that subsequently emerges as recurrent tumor at local or distant sites.

Through a series of well-designed experiments and adept analysis of human breast cancer datasets, the authors demonstrate that downregulation of Par-4 expression is an absolute prerequisite for tumor recurrence and conclude that low Par-4 expression is an independent predictor of decreased recurrence-free survival in women with breast cancer, which corroborates the findings from previous studies [8,9]. This is further exemplified by the finding that highly aggressive, estrogen receptor-negative, high-grade (grade 3), and basal-like tumors exhibit extremely low levels of Par-4.

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## The viewpoint

Various other studies have described the loss, down-regulation, or inactivation of Par-4 in different tumor scenarios [10]. Oncogenic Ras has been shown to downregulate Par-4 expression through MEK-dependent hypermethylation of the Par-4 promoter [11]; consequently, pancreatic cancers harboring K-ras mutations show diminished expression of Par-4 [12]. In their study, Alvarez and colleagues [6] show that downregulation of Par-4 is 'necessary and sufficient' for breast cancer recurrence, which further underscores the tumor-suppressor function of Par-4. However, the mechanism by which Par-4 is downregulated in recurrent breast tumors is yet to be elucidated. Identifying this mechanism could provide new insights into oncogenic regulation of Par-4 in the context of breast cancer, making it a promising area for future research.

The article by Alvarez and colleagues [6] makes a valuable contribution toward understanding the mechanisms underlying breast cancer recurrence, thereby opening avenues for new treatment possibilities. An increasing number of women are resorting to prophylactic mastectomy [13], a surgical procedure that can have devastating effects on their physical and emotional well-being. Based on the work by Alvarez and colleagues [6], low Par-4 levels in tumor biopsies can be a powerful prognostic marker for breast cancer recurrence. Using such minimally invasive procedures may provide significant clinical benefit by allowing for more effective therapeutic intervention. Such advances may promote more efficacious personalized therapies and, in so doing, subvert the need for prophylactic mastectomies and reduce patient suffering. The importance of Par-4 as a therapeutic agent can be exploited by using appropriate Par-4 delivery systems, specifically into Par-4-deficient cells, thereby restoring chemo-sensitivity and preventing recurrence. The use of such innovative therapeutic approaches is likely to increase overall patient survival and improve the quality of life.

## Competing interests

The authors declare that they have no competing interests.

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