Breast Cancer RESEARCH

VIEWPOINT

MEK inhibition as a strategy for targeting residual breast cancer cells with low DUSP4 expression

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Abstract

Lack of eradication of disseminated breast cancer by chemotherapy is a central clinical problem. Even tumors that show substantial shrinkage after drug treatment frequently relapse and eventually become refractory to all drugs available. The mechanisms underlying this lack of eradication are largely undefined and it is therefore difficult to develop curative strategies using systemic anti-cancer therapy. In a recent article low DUSP4 expression was reported to activate RAS-ERK signaling in residual breast cancer after neoadjuvant chemotherapy. This may be a druggable characteristic because MEK inhibition increases docetaxel sensitivity in a xenograft model.

Background

Many patients with metastatic breast cancer, in particular those with basal-like breast cancer, initially respond to chemotherapy. Unfortunately, tumors are usually not eradicated, and their relapse is very frustrating for patients and their doctors. Why is it so difficult to cure patients who respond to chemotherapy? Several divergent hypotheses have been proposed to explain this setback (reviewed by Borst [1]). They comprise mechanisms such as lack of drug penetrance ('mechanical resistance'), the presence of quiescent cells, intrinsic biochemical defense mechanisms of cancer stem cells, or the selection of cells within a heterogeneous tumor that contain stochastic alterations allowing survival. Not all residual tumor cells that survive chemotherapy are necessarily drug-resistant cells that multiply in the presence of drug. Sharma and colleagues [2] found in several cell lines a small subpopulation of transiently drug-tolerant cells that were associated with reversible chromatin alterations due to increased gene expression of chromatin-modifying genes (for example, the histone H3K demethylase KDM5A/Jarid1A). Dey-Guha and colleagues [3] suggested that slowly cycling G0-like tumor cells, which are the result of occasional asymmetric divisions and feature low AKT signal, contribute to drug tolerance. The clinical observation that some recurrent tumors respond again to the same drug given initially is consistent with the idea that drug-tolerant cells contribute to the lack of tumor eradication in patients. How to target residual cancer cells? Many scientists think that such tumor cells are cancer stem cells, a hypothesis that is under heated debate [4,5]. According to this hypothesis, there is a rare population of cancer cells with self-renewing capacity that needs to be targeted to eradicate the tumor. To attack those cells, inhibitors of signaling pathways that regulate self-renewal of normal somatic stem cells (for example, Wnt, Sonic Hedgehog and Notch pathways) have been proposed [6], but thus far the benefit of this strategy is limited. Obviously, specificity is a problem and it remains to be seen whether recently identified compounds, such as the dopamine receptor antagonist thioridazine [7], will overcome this hurdle.

Article

In a recent report, Balko and colleagues [8] profiled 49 residual breast cancers (enriched for the triple-negative subtype) after neoadjuvant chemotherapy. For this purpose 355 transcripts were quantified using NanoString technology [9]. The selection of probes for this analysis was based on previously published prognostic and predictive breast cancer signatures. Cell proliferation, measured by Ki-67 immunohistochemistry, was applied as a surrogate marker to measure therapy outcome. The authors found that a low expression of the dual specificity protein phosphatase 4 (DUSP4) correlated with a high Ki-67 score. DUSP4 acts as an ERK phosphatase, and DUSP4 loss could indeed be associated with high ERK activity in basal-like breast cancers. Inhibition of *DUSP4* by small interfering RNA reduced the sensitivity of breast cancer cell lines to the microtubule-targeting drug

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docetaxel. Since DUSP4 negatively regulates the RAS-ERK pathway, the authors hypothesize that low DUSP4 expression may be a marker for response to MEK inhibitors. This notion was supported by experiments with xenotransplanted MDA-231 breast cancer cells. These cells show a low expression of DUSP4 and have increased pERK1/2 levels. When the xenotransplants were treated with the MEK inhibitor AZD6244 (selumetinib), docetaxel sensitivity was enhanced.

Viewpoint

The combination of mitogen-activated protein kinase pathway inhibition with chemotherapy remains a hopeful strategy to increase chemotherapy sensitivity of solid tumors. Several promising MEK inhibitors such as PD 0325901 and AZD6244 are currently being tested clinically [10]. Based on the work of Balko and colleagues [8], quantification of *DUSP4* gene expression may be useful to predict whether the RAS-ERK pathway is active and whether a patient may benefit from the combination of a MEK inhibitor with taxane-based chemotherapy. Unfortunately, the precise mechanism how the activated RAS-ERK pathway causes poor drug response is unknown. In this respect, it would be interesting to investigate whether DUSP4 loss also causes resistance to other chemotherapeutic drugs besides docetaxel, such as to DNA alkylating or cross-linking agents.

Cells with low DUSP4 expression show a high Ki-67 score, which is associated with poor long-term outcome after neoadjuvant chemotherapy [11]. Hence, the residual cells that show low DUSP4 expression are not quiescent, drug-tolerant cells. Instead, they appear to be truly drug refractory and proliferate regardless of drug treatment (assuming that no major changes in the Ki-67 score have occurred in the time between the last drug treatment and tumor resection). The hope is that additional MEK inhibition can further slow down the growth of residual breast cancer cells after chemotherapy and provide additional time for patients with metastatic disease. It is questionable, however, whether this strategy is curative. Residual cancer cells may still have another backup: entering a quiescence program and lying low until the drug is gone.

Competing interests

The authors declare that they have no competing interests.

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