

Unsuspected protein determines resistance to breast cancer treatment

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An innovative research approach has identified a previously unsuspected protein as a key player in the resistance to particular forms of breast cancer therapy. The study, published by Cell Press in the February issue of *Cancer Cell*, significantly advances the understanding of the molecular response to breast cancer therapies that target estrogen signaling.

Most breast tumors express estrogen receptor and are dependent on estrogen signaling. Drugs that target this characteristic, such as tamoxifen, have had a major impact on breast cancer therapy as they interfere with the ability of estrogen to activate its receptor and, as a result, limit cellular proliferation.

However, although widely used, the effectiveness of tamoxifen is profoundly limited by the development of drug resistance. "All patients with metastatic disease and 40% of early-stage breast cancer patients treated with tamoxifen eventually relapse with tamoxifen-resistant disease," explains lead author Professor Alan Ashworth from the Breakthrough Breast Cancer Research Centre at The Institute of Cancer Research in London, England.

To develop a better understanding of the molecular events that contribute to the development of treatment resistance, Prof. Ashworth, Dr. Christopher J. Lord and colleagues used a sophisticated and highly selective loss-of-function RNA interference screening method to identify genes that, when silenced, cause tamoxifen resistance. The researchers identified Cyclin-Dependent Kinase 10 (CDK10) as a critical component of the response to tamoxifen and other therapies that target estrogen signaling.

Examination of signaling molecules downstream of CDK10 led the authors to propose that CDK10 normally represses the ETS2 transcription factor and that the loss of CDK10 expression results in

relief of ETS2 repression and upregulation of c-RAF transcription. Enhanced c-RAF activation results in activation of mitogen-activated protein kinase and increased cyclin D1 expression, both previously linked to tamoxifen resistance. Together, these events link tamoxifen with a loss of reliance on estrogen signaling.

Importantly, the researchers also found that in patients treated with tamoxifen, drug resistance occurred significantly earlier in those with tumors that express low levels of CDK10. Furthermore, methylation of the CDK10 gene also correlated with resistance. Methylation of genes is well-established as a means by which gene expression can be controlled and suggests a mechanism that could switch off CDK10 expression in tumor cells.

"Drug resistance is a serious problem for women with breast cancer. It's devastating for a patient to see their cancer return because of resistance, especially after enduring a long course of treatment and after a long period of remission. Through this work, we've identified some of the factors that control this effect and in the future we may be able to use this information to decide which treatments to give to patients to avoid resistance," says Prof. Ashworth.

Source: Cell Press

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