TARGETED THERAPIES

Breast cancer cells—escape artists

Two-thirds of patients with breast cancer overexpress hormone receptors; agents that target these receptors include tamoxifen, fulvestrant and aromatase inhibitors, but many tumors develop resistance to these therapies.

The established mechanism of escape from hormone dependence is HER2 overexpression, but this occurs in less than 10% of patients. Researchers led by Carlos Arteaga studied alternative mechanisms in four breast cancer cell lines that had long-term estrogen-deprivation.

The team identified amplification of the PI3K/AKT/mTOR pathway in all the cell lines using proteomic and gene-expression profiling, indicating that the escape from hormone dependence was associated with hyperactivation of the insulin growth factor receptor 1 (IGF-IR), insulin receptor and PI3K/AKT pathway.

Further analysis of 64 estrogen receptor (ER)-positive tumors demonstrated significant correlation between the ratio of total to phosphorylated IGF-IRβ and disease recurrence after endocrine therapy ($P = 0.036$), as shown in previous studies.

> “...patients who relapse on endocrine therapies may benefit from therapeutics targeting both the ER and PI3K pathways...”

Treatment with the dual PI3K/mTOR inhibitor BEZ235 (Novartis, NJ, USA) efficiently prevented escape in all cell lines. “Our findings suggest that patients with hormone-receptor positive tumors exhibiting a high degree of PI3K signaling, and patients who relapse on endocrine therapies may benefit from therapeutics targeting both the ER and PI3K pathways”, explained Arteaga.

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Original article Miller, T. W. *et al.* Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. *J. Clin. Invest.* **120**, 2406–2413 (2010)