Nature Reviews Cancer | AOP, published online 16 June 2011; doi:10.1038/nrc3097

THERAPEUTIC RESISTANCE

Up or down?

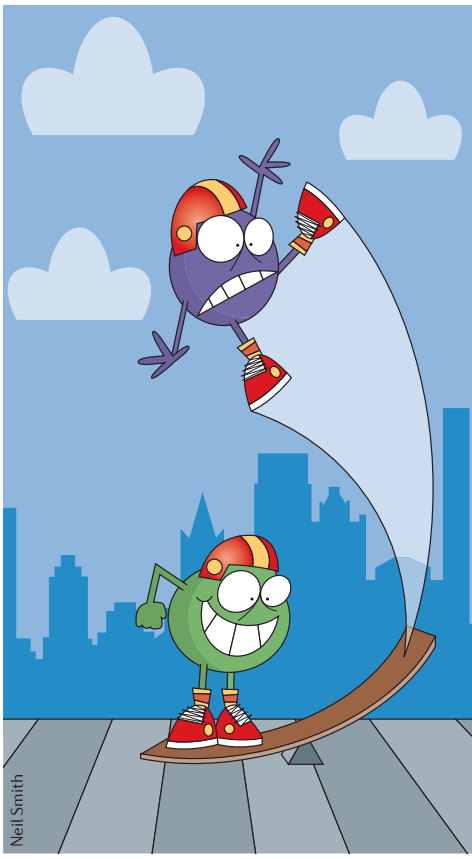
Two papers identify new modulators of oestrogen receptor-α (ERα) expression that have implications for the response of ERα$^+$ breast cancer to endocrine therapy.

Pan, Zhou, Tai and colleagues investigated whether CUE domain-containing 2 (CUEDC2) — which was previously shown to regulate progesterone receptor expression — regulated ERα in breast cancer. Overexpression of CUEDC2 in breast cancer cell lines decreased the levels of ERα, but transcription of *ESR1* (which encodes ERα) was unaffected. The CUEDC2 CUE domain — which binds ubiquitin — was required for the ubiquitylation and degradation of ERα, and CUEDC2 knockdown increased the binding of ERα to the promoters of target genes.

The authors found that CUEDC2 protein and mRNA was significantly overexpressed in breast cancer tissues compared with matched adjacent tissue. Moreover, CUEDC2 expression was inversely correlated with the expression of ERα and progesterone receptor. High CUEDC2 expression in ERα$^+$ tumours (from patients who received tamoxifen) predicted significantly poorer disease-free survival (DFS) and overall survival than did low CUEDC2 expression. CUEDC2 expression did not correlate with the survival of patients with ERα$^-$ tumours who received tamoxifen or for any patient who did not receive tamoxifen. They found that CUEDC2 expression is an independent predictive marker of the outcome to tamoxifen therapy. This indicates that high CUEDC2 expression reduces ERα expression and thereby limits the response to tamoxifen therapy.

To identify kinases that regulate ERα activity, Giamas and colleagues carried out a small interfering RNA screen targeting the human kinome. They found that knockdown of lemur tyrosine kinase 3 (LMTK3) in MCF-7 (ERα$^+$) breast cancer cells reduced the expression and half-life of ERα in a proteasome-dependent manner and reduced the levels of *ESR1* mRNA and protein levels of forkhead box O3 (FOXO3), which transactivates *ESR1*. LMTK3 knockdown increased protein kinase C (PKC)–AKT activity — a pathway that targets FOXO3 for degradation — indicating that LMTK3 also protects FOXO3 from degradation. PKC also targets ERα for degradation, and inhibition of PKC partially rescued the downregulation of ERα when LMTK3 was silenced, indicating that LMTK3 promotes ERα expression by preventing PKC-mediated downregulation of ERα gene and protein expression.

Using 613 breast cancer samples, the authors found that LMTK3 expression was associated with significantly reduced DFS and overall survival. LMTK3 expression also predicted the response to endocrine therapy, and knockdown of LMTK3 (which is expected to reduce ERα expression) in tamoxifen-resistant breast cancer cell lines reduced cell growth when treated with tamoxifen. They also found intronic polymorphisms that were an independent prognostic factor for DFS and overall survival.



These two papers present a paradoxical scenario: CUEDC2 decreases ERα expression, and this seems to reduce responses to endocrine therapy, whereas LMTK3 promotes ERα expression, and this is associated with poor responses to endocrine therapy. Clearly more work is required to understand the regulation of ERα expression and how this affects responses to therapy.

Gemma K. Alderton

ORIGINAL RESEARCH PAPERS Pan, X. *et al.* Elevated expression of CUEDC2 protein confers endocrine resistance in breast cancer. *Nature Med.* **17**, 708–714 (2011) | Giamas, G. *et al.* Kinome screening for regulators of the estrogen receptor identifies LMTK3 as a new therapeutic target in breast cancer. *Nature Med.* **17**, 715–719 (2011)

“Two papers identify new modulators of oestrogen receptor-α (ERα) expression”