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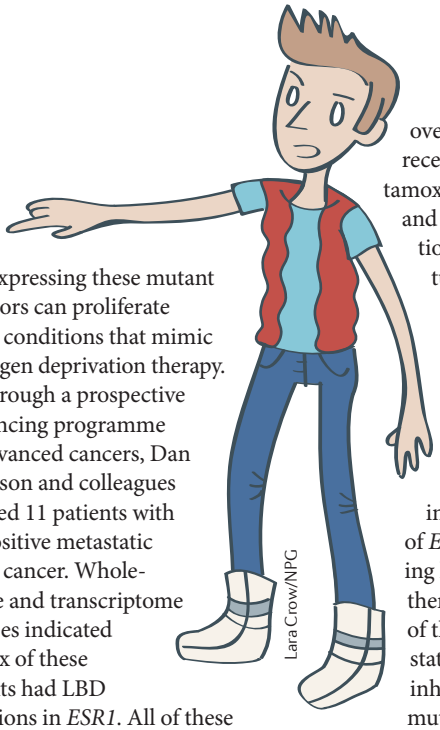
DRUG RESISTANCE

Making a point


Lara Crow/NPG

Resistance to hormone deprivation treatments is a common problem in patients with oestrogen receptor (ER)-positive breast cancer. Three groups have sequenced samples of ER-positive breast cancers and have found point mutations in *ESR1*, the gene encoding ERα, in patients who are refractory to drugs that inhibit the action of oestrogen.

Weiyi Toy and colleagues analysed the genetic changes in two independent cohorts of patients with metastatic ER-positive breast cancer whose disease had progressed during hormone deprivation therapy. They found mutations in the ligand-binding domain (LBD) of *ESR1* in 14 of 80 tumours that resulted in highly recurrent amino acid changes (Tyr537Ser, Tyr537Asn and Asp538Gly). These amino acid changes resulted in an agonist formation of the receptor (an active confirmation normally conferred by ligand binding), and these mutant receptors were able to drive oestrogen signalling pathways and proliferation in the absence of ligand. Moreover, cells expressing these mutated ERs were less responsive to ER antagonists *in vitro* and in mouse xenograft models of breast cancer, indicating that cells expressing these mutant receptors can proliferate under conditions that mimic oestrogen deprivation therapy.

> “mutations in *ESR1* were rare in treatment-naive primary ER-positive breast cancer samples”

Through a prospective sequencing programme for advanced cancers, Dan Robinson and colleagues enrolled 11 patients with ER-positive metastatic breast cancer. Whole-exome and transcriptome analyses indicated that six of these patients had LBD mutations in *ESR1*. All of these patients had been treated with aromatase inhibitors and other anti-oestrogen therapies. The mutations identified in this study (Leu535Gln, Tyr537Ser, Tyr537Cys, Tyr537Asn and Asp538Gly) also resulted in constitutive receptor activation and the requirement for a higher dose of anti-oestrogens, such as 4-hydroxy-tamoxifen, to achieve half-maximal receptor inhibition. Similar findings were reported by Keren Merenbakh-Lamin and colleagues who analysed 15 patients with metastatic breast cancer. Five of the patients had the Asp538Gly ERα mutation in liver metastases, and breast cancer cells overexpressing this mutant receptor were resistant to tamoxifen. Again, structural and biological investigations revealed a constitutively active receptor conformation.

Importantly, all three papers reported that mutations in *ESR1* were rare in treatment-naive primary ER-positive breast cancer samples, indicating that mutation of *ESR1* is selected for during hormone deprivation therapy, possibly as a result of the reduced oestrogen state produced by aromatase inhibitors. As all of these mutated receptors remain responsive to tamoxifen and other oestrogen blockers, more potent drugs, or monitoring patients for the initial detection of clones with *ESR1* mutations, might provide routes to overcome or prevent resistance.

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ORIGINAL RESEARCH PAPERS Toy, W. *et al.* *ESR1* ligand-binding domain mutations in hormone-resistant breast cancer. *Nature Genet.* http://dx.doi.org/10.1038/ng.2822 (2013) | Robinson, D. R. *et al.* Activating *ESR1* mutations in hormone-resistant metastatic breast cancer. *Nature Genet.* http://dx.doi.org/10.1038/ng.2823 (2013) | Merenbakh-Lamin, K. *et al.* D538G mutation in estrogen receptor-α: A novel mechanism for acquired endocrine resistance in breast cancer. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-13-1197 (2013)

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