GENETICS

Switching on the oestrogen receptor

In the past decade, advances in the development of targeted therapies have allowed patients with breast cancer who harbour mutations in the oestrogen receptor (ER) to benefit from treatment with ER inhibitors, such as those that inhibit oestrogen production (aromatase inhibitors) as well as those that block the receptor (tamoxifen). Unfortunately, some patients develop resistance after long-term exposure to these drugs.

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Now, two independent studies published in *Nature Genetics* have identified a type of mutation that arises after hormonal therapy and that could explain why patients often become resistant to this treatment.

Chandarlapaty and colleagues sequenced 80 metastatic breast tumours resistant to hormonal therapy and identified mutations in the *ESR1* gene in 14 of the tumours—all of which were from patients who had been treated with aromatase inhibitors. All the mutations were in the region that encodes for the ligand-binding domain (LBD). Interestingly, untreated metastatic breast tumours did not show mutations in LBD. The authors then sought to identify how these mutations conferred resistance to hormonal therapy and found that, in cells that do not express ER, expression of the mutant forms of LBD translated into a constitutive activation of the receptor—even in the absence of ligand (oestradiol)—that was much more potent than the wild-type receptor. Importantly, tamoxifen was able to inhibit the activity of LBD mutants.

Similarly, Robinson *et al.* sequenced 11 metastatic breast tumours previously treated with anti-oestrogens and aromatase inhibitors, and identified mutations in *ESR1* in six of them, also in the LBD region.

“This is the tumour’s way of evading hormonal therapy. These mutations activate the ER when there is no oestrogen—as is the case when a patient takes an aromatase inhibitor. It’s essentially an ‘on’ switch for the ER,” says Robinson. Constitutive activation of mutant ER was also inhibited by tamoxifen in this study.

These findings suggest that patients who develop resistance to aromatase inhibitors might respond to antioestrogen therapy, such as tamoxifen or fulvestrant, although “such doses may not be achievable in humans”, notes Chandarlapaty.

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Original articles Toy, W. *et al.* *ESR1* ligand-binding domain mutations in hormone-resistant breast cancer. *Nat. Genet.* doi:10.1038/ng.2822 | Robinson, D. R. *et al.* Activating *ESR1* mutations in hormone-resistant metastatic breast cancer. *Nat. Genet.* doi:10.1038/ng.2823