Neuregulin: a cut-and-pasted cancer gene?

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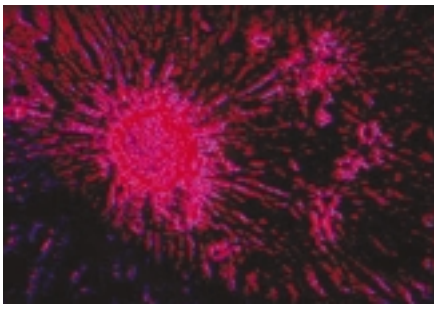
Researchers in France and the UK have identified a recurrent chromosome translocation breakpoint in breast cancer cell lines. The chromosome 8 breakpoint is within the *NRG1* gene, which encodes growth factors belonging to the neuregulin/heregulin-1 family [1].

'The involvement of the *NRG1* gene in oncogenesis and the association of its gene product with ERBB receptors,' says Max Chaffanet, Head of the Molecular Cytogenetics Laboratory at the Institut Paoli-Calmettes (http://www.institutpaolicalmettes.fr), 'suggest that *NRG1* may be a good candidate for new therapeutic applications.' In addition, notes Paul Edwards, senior lecturer in molecular cellular pathology at the University of Cambridge (http://www.path.cam.ac.uk/~pawe1/home-page.html), 'our discovery could extend the range of breast cancers that would benefit from treatment with Herceptin®,' a monoclonal antibody currently used to treat breast cancers that overexpress ERBB2.

The breast cancer problem

Breast cancer is the second most common cancer to affect women in developed countries. Current treatments for the disease rely mainly on radiotherapy and chemotherapy. However, 25–30% of breast tumours overexpress a tyrosine kinase receptor known as HER-2 or ERBB2 and, for these patients, treatment with Herceptin® can be beneficial [2]. ERBB2 is the co-receptor for neuregulin [3], its receptors being ERBB3 and ERBB4 and, says, Ruth Lupu, Director of Breast



Cancer Translational Research at the Evanston Northwestern Healthcare Institute (http://www.enh.org/research/index.asp), 'up to 30% of invasive breast tumours overexpress neuregulin'.

Why look for chromosome translocations?

For years, scientists have been searching the complex karyotypes of breast cancers for characteristic genetic changes that might pinpoint the genes involved in breast cancer development. However, little attention has been paid to the possibility that solid tumours might have recurrent chromosome translocations.

'If you develop leukaemia,' explains Edwards, 'one of the first things the clinicians do is to look at the chromosomes in your tumour to help them decide what sort of leukaemia it is and what type of treatment to give you.' For example, the characteristic chromosome translocation in chronic myeloid leukaemia produces a constitutively active tyrosine kinase BCR/ABL, which can be inhibited by the specific tyrosine kinase inhibitor Gleevec. But, says Edwards, 'if you have a solid tumour, it is not even technically possible to look at the chromosomes yet'.

This situation is now changing, at least in research laboratories. The first step towards discovering translocations in breast cancer, explains Chaffanet, is to use multicolour fluorescence *in situ* hybridization (FISH) to examine metaphase spreads from tumour cell lines. Each chromosome is 'painted' a different colour through hybridization with probes that are specific for each chromosome and translocations show up as chromosomes in which two colours are juxtaposed. 'The karyotypes we saw were complex,' notes Chaffanet, 'but often involved chromosome 8.'

Homing in on the breakpoint

To discover the exact site of the chromosome 8 breaks, the researchers turned to two-colour FISH. 'We have access to a fantastic resource consisting of overlapping BACs [bacterial artificial chromosomes] from the human genome project,' explains Edwards, 'so we can do FISH with pairs of BACs that are in the region of the breakpoint and look for examples of pairs in which only one partner hybridizes to chromosome 8. These two BACs have to span the actual breakpoint and we can then use intervening BACs to map it in detail.'

Out of 34 breast cancer cell lines examined, the researchers found that five had breakpoints within a 1.1 Mb region containing the *NRG1* gene [1]. 'This thorough survey establishes that, at least in breast cancer cell lines, there is a common breakpoint that is worth investigating further,' says David F. Stern, Professor of Pathology at Yale University (http://www.yalepath.org/DEPT/labs/stern/sternlab.htm).

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'However, the result needs to be extended to actual tumours, and the functional consequences of this translocation on neuregulin expression and/or structure remain to be determined, as does the partner gene for *NRG1* in the translocation. As the authors discuss, this may be as important as *NRG1* for oncogenesis.'

The therapeutic potential

Edwards and Chaffanet are tackling these outstanding questions and agree that for now neuregulin can only be a tentative therapeutic target for breast cancer. 'However, we already know that one breast cancer cell line secretes a fused neuregulin that is a stimulatory ligand for the ERBB family of receptors,' says Edwards [4], and Lupu recently reported that breast cancer tumorigenicity and metastasis can be inhibited by blocking neuregulin expression [5], results that indicate that targeting neuregulin function might be useful therapeutically.

More immediately, these new results might prompt a rethink in how Herceptin® is used. At present, says Lupu, 'only patients whose tumours overexpress ERBB2 are known to benefit from Herceptin® treatment.' However, if alterations in neuregulin, possibly caused by chromosome translocations, lead to activation of ERBB2, then additional patients might benefit. To test this, Lupu is retrospectively measuring not only the expression of ERBB2 but also its activation and neuregulin expression in patient samples to see whether either of these additional parameters correlates with a good response to Herceptin®. Edwards, meanwhile, wants to examine gene expression patterns in tumours with chromosomal breakpoints within *NRG1*. 'We may find that these tumours look very much like ERBB2 overexpressors but have normal levels of ERBB2, and patients with this type of tumour may benefit from Herceptin® treatment,' he speculates.

Finally, it seems likely that recurrent chromosomal breakpoints will also occur only in other solid tumours. Indeed, Edwards and Chaffanet discovered *NRG1* specific translocations in two pancreatic cancer cell lines during their studies. 'Given our results,' says Edwards, 'I am sure more people will start to look for and find this type of chromosome rearrangement in other carcinomas,' the hope being that this new information will uncover new therapeutic targets.

References

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Promoting proteasomes: trash to treasure

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Until recently, proteasomes were either on or off. Now, however, researchers have discovered a novel class of proteasome inhibitors with a unique mechanism-of-action that offers the potential for more substrate-specific regulation of proteasome activity. This could lead to the development of new drugs for treating heart disease, stroke and inflammation [1].

Not just a trash can

Proteasomes are large, multisubunit protease complexes that have long been considered to be simple intracellular waste disposal units, merely gobbling and chewing up proteins that are old, damaged or no longer useful. The 26S assembly is comprised of a 20S cylinder, containing four stacked rings, with two 19S 'lids' (see Figure 1).

The lids perform a regulatory function by recognizing those proteins that have been marked for degradation with ubiquitin and granting them entrance into the cylinder. Inside the cylinder, β-subunits form the proteolytic core where active centres actually digest the proteins, resulting in short peptide fragments; outside, α-subunits maintain the shape of the cylinder.

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