ANTICANCER DRUGS

Collusion

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10.1038/nrd2276

URLs

ERBB2
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=2064

ERBB3
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=2065

PTPN1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=5770

Breast cancer
http://www.cancer.gov/cancertopics/types/breast/

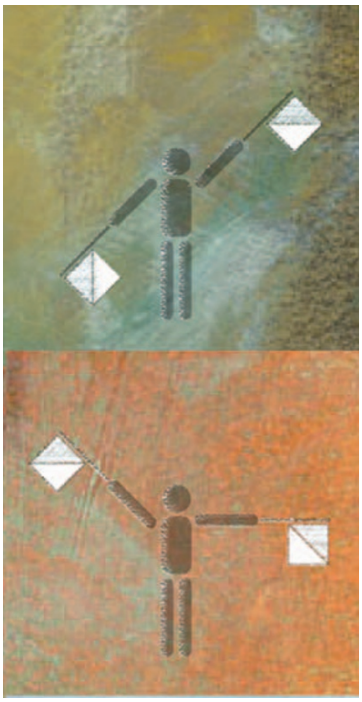
Approximately 25% of breast cancers overexpress the protein tyrosine kinase ERBB2, and their dependence on its expression has been verified through the clinical success of the anti-ERBB2 antibody trastuzumab. However, single agents are often at risk of driving the selection of resistant clones, and Michel L. Tremblay and colleagues have found that inhibition of the protein tyrosine phosphatase PTPN1 (also known as PTP1B) could improve anti-ERRB2 therapies.

ERBB2 is mutated and activated in breast cancer owing to mutations in either the tyrosine kinase domain or the extracellular domain (ECD). 90% of tumours that overexpress ERBB2, and 40% of all human breast tumours, also overexpress PTPN1, and the expression of an ECD mutant ERBB2 in normal human breast epithelial cells also induces PTPN1 expression. However, PTPN1 is also known to suppress tyrosine kinase activity. To address this paradox, Tremblay and colleagues generated transgenic mice that express this specific ECD mutant in breast epithelial tissue under the control of the mouse mammary tumour virus (MMTV-NDL2 mice) and crossed them with *Ptpn1*-null mice to analyse the contribution of PTPN1 to ERRB2-induced breast tumours.

They found that the loss of PTPN1 significantly delayed the onset of breast tumour development and also suppressed the development of lung metastases that are often seen in MMTV-NDL2 mice. Moreover, histopathological analysis showed that the loss of PTPN1 delays the transition between hyperplasia and carcinoma *in situ*. ERBB2 can form a highly active signalling heterodimer with ERBB3, and levels of ERBB3 were reduced in *Ptpn1*-null mice. Downstream signalling pathways such as Ras–mitogen activated protein kinase (MAPK) and phosphatidylinositol 3 kinase (PI3K)–Akt were also attenuated, indicating that the loss of PTPN1 blunts both proliferative and anti-apoptotic pathways. The authors also overexpressed *Ptpn1* in breast epithelial tissue in mice, and showed that PTPN1 is oncogenic in this tissue.

So, is PTPN1 a good drug target for ERBB2-positive breast cancer? The authors treated NDL2 mice with a specific, orally available PTPN1 inhibitor and found that this too significantly delayed breast tumour development.

Although the inhibition of PTPN1 is an attractive possibility for the treatment of early ERBB2-positive breast cancer, particularly those tumours that become resistant to trastuzumab, it will be interesting to see if it is also efficacious for more advanced disease.



Nicola McCarthy
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ORIGINAL RESEARCH PAPER Julien, S. G. *et al.* Protein tyrosine phosphatase 1B deficiency or inhibition delays ErbB2-induced mammary tumorigenesis and protects from lung metastasis. *Nature Genet.* 28 January 2007 (doi: 10.1038/ng1936)