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BREAST CANCER

SRC hits the mark

Trastuzumab (Herceptin; Genentech) is a therapeutic monoclonal antibody targeting ERBB2 (also known as HER2), a receptor tyrosine kinase (RTK) that is overexpressed in ~30% of breast cancers. Various molecular mechanisms of *de novo* and acquired resistance are major limitations of the clinical efficacy of this and other anticancer therapies. Such resistance may underlie the problem that, although initially effective at controlling disease, trastuzumab offers only a minor overall survival benefit to patients. However, a new study shows that the SRC oncoprotein may represent a universal signalling node, the targeting of which can overcome multiple mechanisms of trastuzumab resistance.

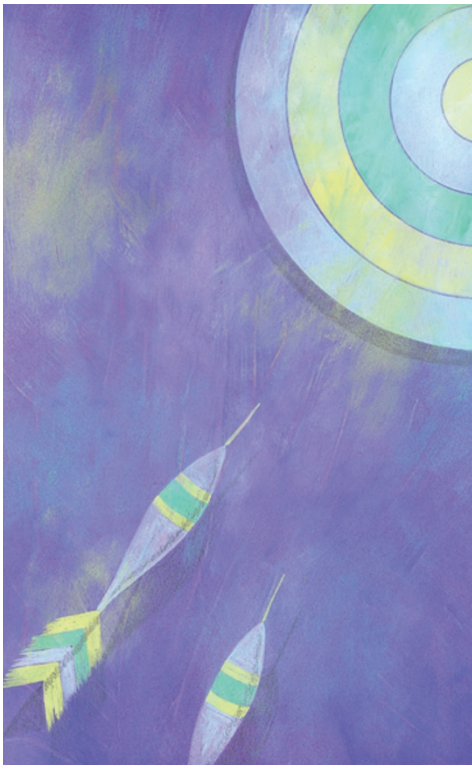
Dihua Yu and colleagues analysed trastuzumab resistance in various ERBB2-overexpressing breast cancer cell lines and, as expected, resistance mechanisms were heterogeneous. After long-term exposure to trastuzumab, different cell lines acquired a range of RTK signalling alterations, including downregulation of ERBB2 and hyperactivation of epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF1R) or ERBB3. Additionally, loss of PTEN function, as occurs in a subset of ERBB2-overexpressing breast cancers (and the cell line MDA-MB-468), resulted in *de novo* trastuzumab resistance.

Despite the heterogeneity of these resistance mechanisms, a comparison of signalling between sensitive and resistant cell line pairs revealed that hyperactivation of SRC (as shown by SRC Tyr416 phosphorylation) in resistant cells was surprisingly universal. Interestingly, the authors demonstrated that the Tyr416 phosphate of activated SRC is a direct substrate for the PTEN phosphatase, explaining how loss of PTEN can result in SRC activation.

Confirming the central role of SRC in trastuzumab resistance, ectopic expression of a constitutively active SRC mutant was sufficient for the induction of trastuzumab resistance, both in cell lines and in xenografted tumours. Further analyses indicated that SRC signalling was in a positive feedback loop with RTKs such as EGFR, thus bypassing the requirement for ERBB2 signalling. Highlighting the clinical relevance of these studies, a retrospective analysis of patient responses revealed that tumours displaying high levels of Tyr416-phosphorylated SRC had poorer responses to trastuzumab.

Can these findings be harnessed to overcome trastuzumab resistance? Knockdown or chemical inhibition of SRC successfully resensitized resistant cells and xenografts to trastuzumab treatment, producing an apoptotic response. Crucially, this resensitization was independent of the upstream resistance mechanism.

> “Crucially, the resensitization was independent of the causative resistance mechanism.”



It will be interesting to determine whether the activation of SRC can also mediate resistance to small-molecule inhibitors of ERBB2 (such as, lapatinib (Tyverb; GlaxoSmithKline)), or to inhibitors of other RTKs. Finally, it remains to be seen whether the combined targeting of ERBB2 and SRC is well-tolerated and effective in patients with ERBB2-overexpressing breast cancer.

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ORIGINAL RESEARCH PAPER Zhang, S. *et al.* Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways. *Nature Med.* 13 Mar 2011 (doi:10.1038/nm.2309)