DRUG RESISTANCE

Alternative routes

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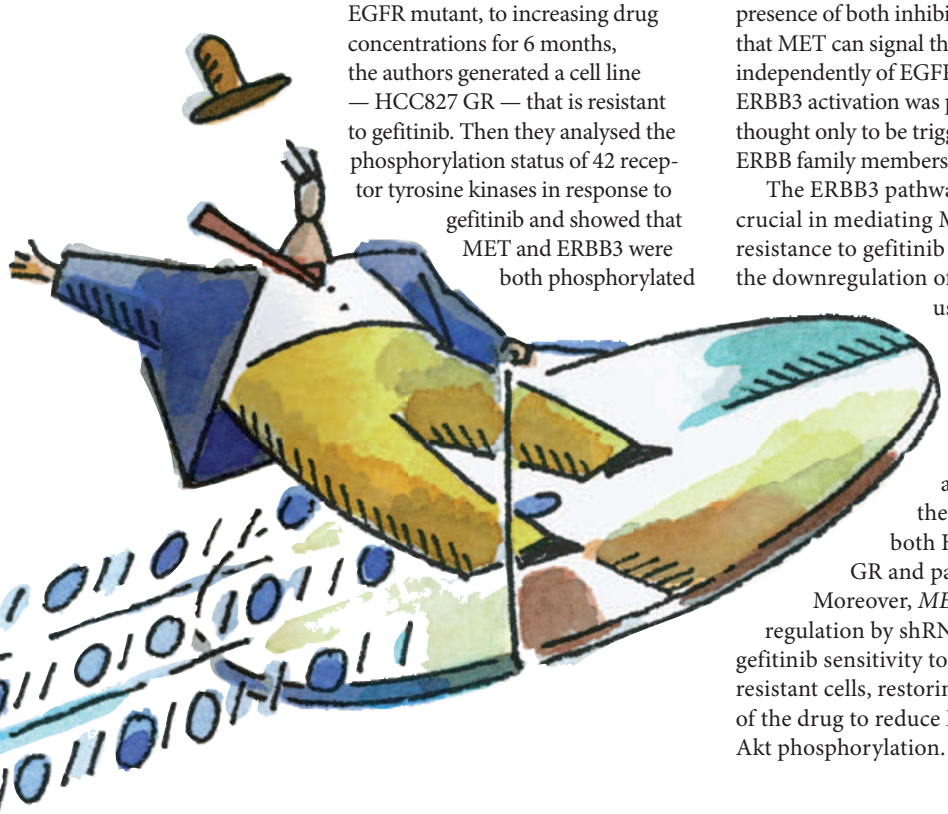
URLs

EGFR
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1956

MET
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4233

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



Two tyrosine kinase inhibitors (TKIs) — gefitinib (Iressa) and erlotinib (Tarceva) — are used to treat non-small-cell lung cancers (NSCLCs) with activating mutations of the epidermal growth factor receptor (EGFR). However, following an initial positive response most tumours become resistant to the drugs; in ~50% of cases this occurs because a secondary *EGFR* mutation arises. Now Jeffrey Engelman and colleagues have identified another route, which involves the amplification of the receptor tyrosine kinase *MET*. This bypasses EGFR inhibition and confers resistance to gefitinib, reactivating the EGFR signalling pathway through the EGFR family member ERBB3.

By exposing NSCLC cells, which express a gefitinib-hypersensitive EGFR mutant, to increasing drug concentrations for 6 months, the authors generated a cell line — HCC827 GR — that is resistant to gefitinib. Then they analysed the phosphorylation status of 42 receptor tyrosine kinases in response to gefitinib and showed that MET and ERBB3 were both phosphorylated in HCC827 GR cells, and their phosphorylation persisted during gefitinib treatment, whereas it was reduced in parental cells. A genome-wide copy number analysis showed amplification of the 7q31.1–7q33.3 locus, where *MET* resides, and quantitative PCR confirmed that *MET* expression was increased in the resistant cells. Sequence analysis ruled out the presence of *MET* mutations in these cells.

MET signalling is indeed required for the acquired gefitinib resistance of HCC827 GR cells because the use of a MET inhibitor, PHA-665,752, in combination with gefitinib treatment, reduced ERBB3 and Akt phosphorylation, resulting in growth inhibition and apoptosis. Interestingly, phosphorylation of ERBB3 in HCC827 GR cells was suppressed only in the presence of both inhibitors, indicating that MET can signal through ERBB3 independently of EGFR, whereas ERBB3 activation was previously thought only to be triggered by other ERBB family members.

The ERBB3 pathway seems to be crucial in mediating MET-induced resistance to gefitinib because the downregulation of *ERBB3*, using short hairpin RNA (shRNA), inhibited Akt phosphorylation and reduced the growth of both HCC827 GR and parental cells. Moreover, *MET* downregulation by shRNAs conferred gefitinib sensitivity to the otherwise resistant cells, restoring the ability of the drug to reduce ERBB3 and Akt phosphorylation.

The finding that *MET* amplification leads to sustained activation of the phosphatidylinositol 3-kinase (PI3K)–Akt pathway by inducing persistent ERBB3 phosphorylation seems common to other tumours. The authors in fact showed that two gastric cancer cell lines harbouring *MET* amplification had high levels of ERBB3 in complex with the p85 regulatory subunit of PI3K, and these complexes were disrupted by PHA-665,752.

Does this resistance mechanism also occur in patients? Notably, 4 out of 18 NSCLCs that were resistant to gefitinib or erlotinib treatment showed *MET* amplification, and only one of these cases had a concomitant secondary mutation of EGFR.

The finding that NSCLCs can escape gefitinib inhibition through the amplification of *MET*, which is not the direct target of the drug, has several implications. It highlights the importance of searching for other genetic alterations, besides *EGFR*, that might be responsible for gefitinib and erlotinib resistance in NSCLCs. It also suggests that MET inhibitors, which are currently being tested in early phase clinical trials, might be effective in combination with EGFR inhibitors in treating at least a subset of resistant tumours. Finally, it raises the possibility that *MET* amplification might induce drug resistance in other EGFR-dependent tumours.

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ORIGINAL RESEARCH PAPER Engelman, J. A. *et al.* *MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 26 April 2007 (doi: 10.1126/science.1141478)
FURTHER READING Sharma, S. V., Bell, D. W., Settleman J. & Haber, D. A. Epidermal growth factor receptor mutations in lung cancer. *Nature Rev. Cancer* **7**, 169–181 (2007)