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KINASES

Overcoming inhibition

Cancers evolve in Darwinian manner: random mutations that confer a reproductive advantage on cell lineages are selected in the highly competitive environment of the tumour. Such evolution can lead to the emergence of altered protein targets that are resistant to the therapeutic drugs used to fight cancer, with a consequent diminution in their efficacy. Writing in *Chemistry & Biology*, Henrik Daub and colleagues now describe a conserved structural determinant that governs the sensitivity of protein kinases to inhibition by small molecules. Their findings could have important implications for the future clinical success of inhibitors of protein kinases, and the development of targeted cancer therapies.

The aberrant functioning of protein kinases is important in oncogenesis, and two well-known anticancer drugs — STI571 (Gleevec; Novartis) and gefitinib (Iressa; AstraZeneca) — target protein tyrosine kinases. Resistance to these drugs is of immediate therapeutic relevance, and has been observed in the case of STI571. Could resistance emerge against other drugs, such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib?

To address this question, Daub and coworkers undertook a mutational analysis of four disease-relevant tyrosine kinases (including EGFR), and screened these mutants against a selection of structurally distinct

inhibitors (including STI571 and gefitinib) to identify structural determinants of drug sensitivity.

In each kinase, a binding pocket at the ATP-binding site was altered; specifically, a conserved threonine residue, an amino acid with a small side chain, was replaced with various other larger amino acids, which blocked access to a cavity at the ATP-binding site. It has already been determined that substituting Thr315 at the ATP-binding site of the ABL kinase with a larger amino acid leads to insensitivity to STI571, and that the equivalent threonine in EGFR, Thr766, is a crucial structural determinant of sensitivity to the small-molecule inhibitor PD153035, which is structurally related to gefitinib.

Daub and colleagues found that the equivalent threonines determined the sensitivities for several inhibitor classes tested, with the exception of indolinone inhibitors (which do not need to extend past the large residue into the back pocket of the ATP-binding site to exert their effects). The substitution of threonine with a larger residue rendered the kinases insensitive to inhibitors, but did not affect their kinase activity. Of particular interest, the replacement of Thr766 of EGFR with methionine led to insensitivity to gefitinib. The nucleotide change in the *EGFR* gene that leads to this substitution occurs in a mutational hotspot, thereby increasing the probability of this mutation arising; © 2004 Nature Publishing Group

the clinical relevance of this remains to be determined.

This research raises the concern that protein kinases could, in general, suffer from the problem of drug resistance seen with STI571. Whether or not indolinone-based drugs could obviate this problem in the clinic remains an open question.

Daniel Jones

References and links

ORIGINAL RESEARCH PAPER Blencke, S. et al. Characterization of a conserved structural determinant controlling protein kinase sensitivity to selective inhibitors. *Chem. Biol.* **11**, 691–701 (2004)