KINASE INHIBITORS

Comparison shopping

The ability to inactivate multiple kinases is a desirable feature of a small-molecule inhibitor, as indicated by the widespread clinical efficacy of imatinib (Glivec). Is it possible to design drugs to have this characteristic? James Brown and colleagues have performed evolutionary analyses of Aurora-kinase sequences — particularly of ATP-binding domains — to uncover the best approach to target multiple members of this family.

The Aurora family of serine/threonine kinases regulate cell division and their expression levels are altered in various tumour types. Pharmaceutical companies have been developing small molecules that target the ATP-binding domain of these proteins, and these drugs can disrupt tumour-cell proliferation *in vitro* and *in vivo*. Mammals have Aurora-A, Aurora-B and Aurora-C, whereas frogs, fruitflies and nematodes carry only Aurora-A and -B. Fungi express a single Aurora homologue. Brown *et al.* analysed the sequences of all these various homologues to determine which protein domains are most closely related to the human genes, and might therefore be the best to study in animal models and in the design of inhibitors.

They found that although Aurora-A is ubiquitous among all vertebrates, Aurora-B and -C arose from a gene duplication in mammals. A comparison of the ATP-binding domains revealed that a stretch of 26 amino acids in the active site was identical between the human homologues of Aurora-B and -C, and varied by only 3 residues in Aurora-A. Inhibitors designed to target this region are likely to block the function of two or possibly all three of these enzymes, and might therefore be less susceptible to tumour resistance.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Brown, J. R. *et al*. Evolutionary relationships of Aurora kinases: Implications for model organism studies and the development of anti-cancer drugs. *BMC Evol. Biol.* **4**, 39 (2004)

FURTHER READING Keen, N. & Taylor, N. Aurora-kinase inhibitors as anticancer agents. *Nature Rev. Cancer* **4**, 927–936 (2004)

KINASE INHIBITION

Life and LYN

The association between BCR–ABL1 expression and chronic myelogenous leukaemia (CML) has been well documented, but there has been debate over the mechanisms by which this chromosome-translocation product mediates cell transformation. In *Nature Medicine*, Andrzej Ptasznik *et al.* report that one of these is likely to include the ability of BCR–ABL1 to interact with the tyrosine kinase LYN to promote cell survival.

Leukaemia cells that express BCR–ABL1 are resistant to apoptotic stimuli, and are therefore resistant to standard chemotherapy. Although patients with CML in its chronic stages can be treated by allogeneic stem-cell transplantation or imatinib (Glivec), this disease becomes more difficult to treat once it reaches the blast crisis stage, during which the leukaemic cells become drug resistant and more aggressive.

BCR–ABL1 interacts with several cell signalling proteins to alter a range of cellular functions. One of its downstream effectors, the SRC family member LYN, becomes activated during the blast crisis stage of CML. It could therefore be an important therapeutic target for patients with late-stage disease.

Using short interfering RNA (siRNA), Ptasznik *et al.* showed that LYN expression could be inhibited by up to 95% in a BCR–ABL1-positive myeloid cell line, in normal haematopoietic cells and also in primary lymphoid and myeloid CML blast crisis cells. Whereas this loss of LYN had no effect on normal cells, the tumour cell types underwent a rapid and massive induction of apoptosis. Primary leukaemia cells derived from both imatinib-resistant and non-resistant patients with CML in the blast crisis stage were particularly sensitive to LYN ablation — over 90% of cells underwent apoptosis. Leukaemia cells from patients in myeloid blast crisis were less sensitive, as their viability was reduced by about 50%.

This study is the first to use siRNA to validate therapeutic targets in primary leukaemia cells, and the authors suggest that this approach might also be developed for therapeutic use. Most importantly, the findings establish LYN as a key target for treating patients with blast crisis stage CML.

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References and links

ORIGINAL RESEARCH PAPER Ptasznik, A. *et al*. Short interfering RNA (siRNA) targeting of the Lyn kinase induces apoptosis in primary, and drug-resistant, BCR–ABL1$^+$ leukemia cells. *Nature Med.* **10**, 1187–1189 (2004)