TECHNOLOGY

Indirect activation

Tyrosine kinase activation is an important oncogenic mechanism; however, it can be difficult to detect indirect mechanisms of tyrosine kinase activation that are not caused by sequence changes in the kinases themselves. A recent study describes a new high-throughput, cost-effective approach that can systematically identify activated tyrosine kinases in cancer cells irrespective of the mechanism of kinase activation.

Most tyrosine kinases are tyrosine phosphorylated after activation, enabling Todd Golub and colleagues to use this phosphorylation status as a marker of activation. They coupled tyrosine kinase-specific antibodies to polystyrene beads, allowing affinity purification of tyrosine kinases from cancer cell lines or tumour samples. An anti-phosphotyrosine antibody was then used to detect the bead complexes that contained activated kinases by flow cytometry.

The authors profiled 130 human cancer lines, creating a tyrosine kinase activation catalogue. They validated their method by detecting the expected patterns of tyrosine phosphorylation in particular cancer cell types, such as *ABL1* phosphorylation in chronic myeloid leukaemia cells containing a *BCR-ABL1* translocation.

To determine whether their assay could be used to identify new therapeutic targets, the authors extended their experiments to the tyrosine kinase *SRC*. They found that *SRC* is activated in glioblastoma cell lines and tumour samples, and that *dasatinib* (which inhibits the *Src* family and several other tyrosine kinases) inhibited proliferation, induced apoptosis and inhibited cell migration in glioblastoma cell lines. Tumour growth was also significantly attenuated when they treated a mouse xenograft glioblastoma model

with dasatinib.

Importantly, the role of *SRC* in glioblastoma was not obvious from analyses of DNA sequence or gene copy number, and was only revealed by analysis of tyrosine phosphorylation status.

The method developed by Golub *et al.*, therefore, establishes the feasibility of large-scale profiling of tyrosine kinase activation, and the principles outlined in this study could be applied to the profiling of other kinases involved in human cancers.

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ORIGINAL RESEARCH PAPER Du, J. *et al.*
Bead-based profiling of tyrosine kinase phosphorylation identifies *SRC* as a potential target for glioblastoma therapy. *Nature Biotech.* 21 Dec 2008 (doi: 10.1038/nbt.1513)