

 CANCER GENOMICS

A modular approach to signalling

Instead of considering signalling in terms of a linear sequence, the concept of modules as units of signalling activity is a useful way to represent complex biological networks, such as those involved in cancer. A recent study describes an approach to dissect oncogenic signalling pathways into functional modules on the basis of gene expression signatures, which can then be used to analyse disease outcome and responses to therapeutics.

Joseph Nevins and colleagues reasoned that whole genome expression data could be used to define oncogenic pathway modules. Using the Ras and E2F signalling pathways as examples, they defined a core set of genes for each pathway; for the oncoprotein Ras, these are genes that encode proteins that directly bind to Ras, and those with one degree of separation from Ras in a protein–protein interaction network. Using

the previously generated NCI-60 data set (which is composed of expression profiles of human cancer cell lines from a range of different tissues) as a source of expression data, the authors then used statistical analyses to identify genes related to the core pathway that showed similar variation in their expression as the core genes. This approach allowed them to generate signatures that correspond to sets of genes that share expression patterns.

The authors identified 20 gene signatures in the Ras pathway and 8 signatures in the E2F pathway. By comparing these signatures with the signatures of mutants that selectively activate downstream effectors or to signatures from cells that are sensitive to drugs that target specific pathway members, they could assign the signatures to specific signalling effectors, such as Raf or phosphatidylinositol 3-kinase for Ras signalling and S phase or mitotic events for E2F.

This allowed them to define signalling pathway modules on the basis of expression signatures.

Can module signatures be used to predict clinical outcome? Chang *et al.* analysed the response of colon cancer patients to the epidermal growth factor receptor (EGFR)-specific therapy cetuximab. They derived a set of 20 gene expression signatures for EGFR from the NCI-60 expression data, and then compared the EGFR, Ras and E2F signatures to see if they could differentiate between the gene signatures of patients who responded or did not respond to cetuximab. Only the EGFR signatures could distinguish between the two sets of patients, indicating the specificity of each set of signatures for a particular oncogenic signalling pathway. Therefore, the oncogenic module approach can be used to identify clinically relevant tumour phenotypes. In a broader context, a modular model of pathway structure could also be valuable for studying the way that information is transmitted through cellular networks and the relationships between signalling modules and phenotypes.

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DIGITAL VISION

ORIGINAL RESEARCH PAPER Chang J. T. *et al.*
A genomic strategy to elucidate modules of
oncogenic pathway signaling networks. *Mol. Cell*
34, 104–114 (2009).

FURTHER READING Nevins, J. R. & Potti, A.
Mining gene expression profiles: expression
signatures as cancer phenotypes. *Nature Rev.*
Genet. **8**, 601–609 (2007).