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EXPRESSION PROFILING

Order out of chaos

The information available in tumour-gene-expression databases can seem overwhelming, but a recent study shows that important insights into the mechanisms of tumorigenesis can be obtained by data mining. Mark Ewen and colleagues report, in *Cell*, that the oncogenic effect of cyclin D1 might be independent from its cyclin-dependent kinase (CDK) function, and that it involves the transcription factor C/EBP β .

To investigate the function of cyclin D1, the authors overexpressed either the wild-type gene or a mutant that is unable to activate CDK4 in the MCF-7 mammary epithelial cell line. RNA was isolated over a 24-hour period, and was hybridized to microarrays. Surprisingly, expression of the wild-type and mutant genes resulted in similar expression profiles — indicating that the ability of cyclin D1 to activate CDK4 does not determine the expression profile — and allowed the authors to identify a 21-gene signature of cyclin D1 expression.

But is the expression signature significant in human cancer? The authors used a database of gene-expression profiles from 190 tumours, and compared the expression level of cyclin D1 with that of the signature genes using the Kolmogorov–Smirnov non-parametric rank statistic. This analysis confirmed that the 21 genes were significantly correlated with cyclin D1 expression, but also allowed other correlating genes to be identified. Three of the top 50 were transcription factors — the involvement of which was

anticipated because the expression profile developed so quickly following cyclin D1 expression — but further analysis of another 500 tumour specimens narrowed the candidate transcription factor down to one: C/EBP β .

To further pin down the link between cyclin D1 and C/EBP β , the authors performed functional analyses of seven gene promoters that were affected by cyclin D1 by cloning them upstream of the luciferase gene. The responsiveness to cyclin D1 was confirmed in six out of seven promoters. Interestingly, deletion and point-mutation analysis of these promoters revealed that the cyclin D1 responsive sites resembled a C/EBP β recognition site.

The luciferase reporter constructs were used again, but this time to test for the ability of C/EBP β to activate transcription. The wild-type protein actually repressed transcription, but a dominant-negative mutant activated transcription, indicating that C/EBP β is normally a repressor.

As both proteins seem to act through the same sequence, it is likely that the transcriptional activity of cyclin D1 is mediated through C/EBP β and, indeed, loss of C/EBP β prevented transcriptional activation of the promoters in response to cyclin D1. The two proteins also physically interact, so it seems that by binding to C/EBP β , cyclin D1 changes the promoter activity from repression to activation.

Despite their complexity, such databases can be effectively used to obtain mechanistic insight into tumorigenesis, and hopefully will be used more in the future.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Lamb, J. *et al.*
A mechanism of cyclin D1 action encoded in the
patterns of gene expression in human cancer. *Cell*
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WEB SITES

Center for Genome Research: <http://www-genome.wi.mit.edu/cancer/>

Mark Ewen's lab:
<http://www.dfci.harvard.edu/abo/danafarber/detail.asp?PersonID=60&RD=True>