The total number of genes in yeast is unlikely to change as a result of this study — the number of previously predicted genes that turn out to be spurious is likely to be offset by the number of new predictions. The true impact of this study lies in the fact that it describes a method for re-examination of genome annotation that is applicable to other genomes and in its ability to predict the existence of genes that have so far eluded previously known methods.

Magdalena Skipper

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WEB SITE
Michael Snyder's lab:
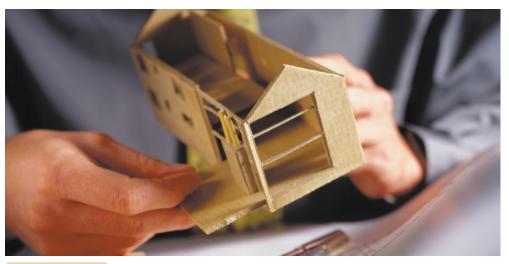http://www.yale.edu/snyder/res.html

together the network of interacting proteins that controls this response, so uncovering many new interactions of probable biological significance.

Although this approach is clearly very powerful, it is not without limitations — for example, Gavin *et al.* could not purify proteins under 15 kDa in size. Both groups also report a significant number of false-positive interactions, while failing to detect some known interactions, perhaps because the tag can interfere with a protein's function or with its physical associations. Although there is still a long way to go before we fully understand how a proteome's functional networks respond to the ever changing life of a cell, these two studies provide a panoramic view of protein function and a wealth of new functional data for genome annotation.

Jane Alfred

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CANCER GENETICS

Intricate modelling

Lung cancer causes most cancer-related deaths worldwide, and of the different lung tumour types, adenocarcinoma is the most common. The involvement of *K-ras* in lung cancer was confirmed last year (see June 2001 Highlights), when Tyler Jacks' group showed that the somatic activation of a constitutively active *K-ras* allele (*K-ras*^{G12D}) can alone cause cancer. This study is now followed up by two new *K-ras*^{G12D} mouse models — one made by Jacks' group and the other by Harold Varmus' group — in which conditional gene-activation systems have been used to switch on this mutant *K-ras* allele. Importantly, these studies shed much needed light on the events required for lung tumour initiation, maintenance and regression, and are a step towards much better mouse models of cancer that can be used to develop and test new cancer therapies.

The gene-expression switches used by each team allowed them to ask different questions about lung tumour biology. Jacks' team used the Cre/*lox*P system to activate *K-ras*^{G12D} by targeting the endogenous *K-ras* locus with a 'lox–stop–lox' (LSL) *K-ras* allele in which *lox*P sites flank a transcriptional Stop element. When Cre was introduced into the lungs of LSL-*K-ras*^{G12D} mice through a nasally delivered adenovirus, their lungs became covered in precancerous lesions within four weeks, and there was evidence that Cre-induced activation of *K-ras*^{G12D} was responsible for this highly penetrant and rapid lung tumorigenesis.

However, such severe tumorigenesis is a problem — in last year's study, for example, the mice developed so many tumours that many died before the earlier lesions could progress to malignancy. The Jacks' group tackled this problem by lowering adenoviral-Cre doses to reduce tumour numbers, allowing the mice to survive and progress to later stages of tumorigenesis. Only then could the team solve the long-standing question of which of several early precancerous lesions give rise to adenocarcinomas — they report that it's most probably a lesion called atypical adenomatous hyperplasia, which seems to originate from one particular cell type, the alveolar type II cell. The

authors also identified a new cell type, possibly a new lung stem cell, that might also contribute to adenocarcinoma development.

Fisher *et al.* used a different trick to turn on the *K-ras*^{G12D} allele — they created bi-transgenic mice that express both a tetracycline (Tet)-activatable form of *K-ras*^{G12D} and a reverse Tet transactivator protein expressed in alveolar type II cells that can only activate *K-ras*^{G12D} in the presence of doxycycline. This elegant approach allowed them to look at the events required for the initiation, maintenance and regression of lung tumours. Within one week of receiving doxycycline in their drinking water, these mice developed hyperplastic alveolar type II cells; after two months, their lungs became laden with large adenomas and adenocarcinomas. Nevertheless, within days of doxycycline withdrawal, these tumours regressed and underwent apoptosis. When these mice were crossed to two mouse strains, each null for a well-known tumour suppressor gene — *Trp53* or *p16*^{ink4a} — they developed more-aggressive tumours much more rapidly. Surprisingly, however, these tumours still underwent rapid apoptosis-mediated regression following doxycycline withdrawal, showing that this regression occurs via a p53-independent apoptotic pathway.

The fact that lung tumours with *p16*^{ink4a} and *Trp53* mutations can be induced to regress is good news indeed for those developing anticancer therapeutics, because *TP53* mutations are associated with tumour resistance to chemotherapy. But what is the pathway that mediates the p53-independent regression of these tumours? Fisher *et al.* have already found some clues to this question in their data, and to investigate it further, they plan to use microarray expression analysis to identify key transcriptional changes that occur during tumour induction and regression in these mice.

Jane Alfred

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WEB SITES
Tyler Jacks' lab: http://mit.edu/biology/www/facultyareas/facresearch/jacks.shtml
Harold Varmus' lab: http://www.ski.edu/lab_homepage.cfm?lab=203