on either, indicating that dephosphorylation of β-catenin is required for activation of β-catenin as a transcription factor. Immunofluorescence revealed that most of the dephospho-β-catenin was nuclear.

These findings are also supported by previously published clinical data: patients whose tumours have high levels of phosphorylated β-catenin have a better prognosis than those with low levels. This extra level of β-catenin regulation might also turn out to be therapeutically useful because it offers hope of blocking β-catenin's transcriptional function even in the absence of active APC.

Cath Brooksbank

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PROGNOSTICS

Tailor-made therapy

A diagnosis of lymph-node-negative breast cancer can result in very different long-term prognoses. The ability to correctly predict the outcome would influence treatment decisions, but how can this be achieved? Laura van't Veer *et al.* report in the 31 January issue of *Nature* that a 'prognosis classifier', identified using microarray analysis, can outperform other clinical methods that are currently used to forecast disease outcome, and could be used to determine whether patients would benefit from adjuvant therapy.

In order to identify a gene-expression signature that could be used to predict disease outcome, the authors isolated RNA from 98 tumours of patients with lymph-node-negative, primary breast cancer. Microarray analysis revealed that 5,000 genes had significant alterations in expression level. An unsupervised cluster analysis — which grouped tumours according to their similarities over these 5,000 genes — then showed that the tumours fell into one of two groups, and that these could, to some extent, distinguish between tumours with a good prognosis and a bad prognosis.

In order to establish a more effective prognostic signature, tumours taken from 78 patients diagnosed with sporadic cancer — 44 of whom had remained disease free for at least 5 years and 34 of whom had developed distant metastases within 5 years — were subjected to a three-step supervised classification method. This allowed identification of 70 genes — the 'prognosis classifier' — that could correctly predict disease outcome in 83% of cases. However, even if this sacrifices overall accuracy, because failure to treat a patient with a poor prognosis is more dangerous than over-treating a patient with a good prognosis, it is more important that the poor-prognosis patients are diagnosed correctly. Altering the threshold to achieve this aim allowed more than 90% of the tumours with a poor prognosis to be assigned correctly.

So which genes predict tumour prognosis? Unsurprisingly, those involved in cell-cycle progression, invasion and metastasis, angiogenesis and signal transduction are upregulated in tumours with a poor prognosis. But interestingly, genes that have previously been suggested to be predictive of breast cancer outcome did not appear in the prognosis classifier, perhaps indicating that single genes are lacking in predictive power and validating the 'multigene' approach.

So how effective is the prognosis classifier compared with more conventional methods of classifying tumours? When tested on an independent set of primary tumours, the disease outcome was correctly predicted for 17/19 patients. Moreover, the poor prognosis signature was shown to result in an odds ratio of 15 for a short time to metastasis (as compared with the good signature tumours). This is a significant improvement on prognostic factors that are currently used, such as tumour size, grade and angioinvasion.

Such prognosis classifiers could be used to aid in treatment decisions — at present, 70–80% of patients that receive adjuvant therapy would have survived without it, and chemotherapy has significant side effects and long-term consequences. This classification method can predict those that should receive treatment as effectively as other methods, while reducing the number who receive treatment unnecessarily. Gene signatures therefore seem to be the way forward in predicting outcome, and should pave the way for new therapies that are tailored to the patient.

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