locations in the AID-overexpressing cells, but no effect was evident in the *Aid*$^{-/-}$ cells. Proteins involved in the non-homologous end-joining (NHEJ) pathway of DNA repair are known to be required for the resolution of the double-strand breaks within the immunoglobulin switch region, but the authors found that the NHEJ pathway was not needed for *Myc–Igh* translocations to occur.

Loss of the DNA-damage transducer ATM, which is required for immunoglobulin class switching, increased the frequency of *Myc–Igh* translocations in AID-expressing cells. Moreover, absence or haploinsufficiency of the tumour suppressor p53 — a downstream target of ATM — led to high levels of *Myc–Igh* translocations. Because the aberrant expression of MYC is known to activate the ARF–p53 tumour-suppressor pathway, the authors also looked for, and found, increased occurrences of *Myc–Igh* translocations in ARF-null B cells. Therefore, the authors conclude that ATM, p53 and ARF are part of the mechanism that detects and protects against the occurrence of *Myc–Igh* translocations. Despite the genomic instability induced by the loss of ATM, the authors found no evidence that genomic instability promotes the formation of *Myc–Igh* translocations.

The authors have proposed a model to account for their findings. Class switching requires the formation of AID-induced DNA double-strand breaks, and these are correctly repaired by the NHEJ system and a host of other proteins involved in the detection and repair of DNA double-strand breaks, including ATM but excluding p53. Lesions that are not resolved induce a p53 response through the activation of ATM. It is the cells that escape this response and make NHEJ-independent translocations that activate the ARF pathway, resulting once again in p53 activation. So, p53 mutation or loss is likely to contribute early on to the pathogenesis of lymphoma by facilitating AID-induced translocations.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Ramiro, A. R. *et al.* Role of genomic instability and p53 in AID-induced c-myc–Igh translocations. *Nature* 8 Jan 2006 (doi: 10.1038/nature04495)

to distinguish patients who respond favourably to chemoradiotherapy from those who do not. So far, neither histological nor demographic factors have been successfully used to make such a distinction.

The authors profiled gene expression in biopsy samples from 19 patients who subsequently underwent chemoradiotherapy. Pathological outcome was estimated by the presence or absence of residual cancer cells in surgical samples that were obtained 5 to 6 weeks after treatment.

An automated analysis based on expression profile alone divided the patients into 2 clear classes of 9 and 10 individuals. This was combined with the pathological outcome data to show that five of the six patients who had no residual cancer belonged to one class. The authors demonstrated that combinations of individual apoptosis and differentiation genes could be used to discriminate between the classes.

The results involve a small sample size and need validating with other patients, but this is the first demonstration of molecular signatures in oesophageal cancer that correlate with treatment response. More and better biomarkers might follow, allowing treatment to be tailored to the individual.

Patrick Goymer

ORIGINAL RESEARCH PAPER Luthra, R. *et al.* Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. *J. Clin. Oncol.* 12 Dec 2005 (doi:10.1200/jco.2005.03.3688)

Trial Watch

PREDICTING TREATMENT OUTCOME

Although leukaemic subtypes with poor prognosis have a decreased tendency to undergo apoptosis, gene-expression-profiling studies have identified few differentially expressed apoptosis genes. William Evans, Rob Pieters and colleagues therefore analysed the expression of 70 key apoptosis genes in leukaemic cells taken from 190 children with acute lymphoblastic leukaemia (ALL).

The authors found differences between the expression profiles of ALL subtypes: 44 genes were differentially expressed in T-lineage versus B-lineage ALL, 22 genes differed in hyperdiploid versus non-hyperdiploid B-lineage ALL, 16 genes differed in TEL–AML1^{+} versus TEL–AML1^{-} B-lineage ALL, and 13 genes differed in E2A-rearranged versus E2A-germline B-lineage ALL. Next, they looked at the differences in expression of apoptotic genes between drug-sensitive and -resistant patients in the B-lineage ALL group. Although no probe sets were associated with resistance to vincristine or daunorubicin, *MCL1* and *DAPK1* were associated with prednisolone resistance, and *BCL2L13*, *HRK* and *TNF* were associated with resistance to L-asparaginase.

BCL2L13 was the only gene independently associated with treatment outcome. The 5-year probability of disease-free survival was 85% for patients with low expression of *BCL2L13* and 66% for patients with high expression. These findings were validated on an independent cohort of 92 patients treated with the same drugs but on a different protocol.

BCL2L13 has pro-apoptotic activity in cell lines, so it is surprising that high expression is associated with drug resistance in this study. The authors suggest that BCL2L13 might have a different apoptotic role in primary leukaemic cells, or that there might be an anti-apoptotic splice variant. Prospective validation is now required to establish BCL2L13 expression as a true prognostic factor in childhood ALL.

ORIGINAL REFERENCE Holleman, A. *et al.* The expression of 70 apoptosis genes in relation to lineage, genetic subtype, cellular drug resistance, and outcome in childhood acute lymphoblastic leukemia. *Blood* **107**, 769–776 (2006)

PREDICTING DISEASE PROGRESSION

The role of ERBB2 (also known as HER2/NEU) is best characterized in breast cancer progression, but overexpression of ERBB2 has also been observed in patients with metastatic androgen-independent prostate cancer. Iman Osman *et al.* analysed the serum of 279 patients enrolled in a prospective serum bank using the FDA-approved Immuno-1 ERBB2 assay.

Increased serum ERBB2 was observed in 13.3% of patients (cut-off value for normal serum was 14 ng ml^{-1}). There was a significant difference between serum ERBB2 concentrations in patients with and without metastases, and the risk of cause-specific death increased with each unit increase in serum ERBB2. These data indicate that this test could be used to identify potential candidates for anti-ERBB2 therapy.

ORIGINAL REFERENCE Osman, I. *et al.* Serum levels of shed HER2/NEU protein in men with prostate cancer correlate with disease progression. *J. Urol.* **174**, 2174–2177 (2005)