LYMPHOMA

Ups and downs

Germinal-centre-derived B-cell lymphomas are commonly associated with chromosome translocations or mutations that activate expression of *BCL6*, which encodes a transcriptional repressor. Very few BCL6 target genes have been identified, however, so it has been unclear how its dysregulation might lead to cancer. In *Nature*, Ryan Phan and Riccardo Dalla-Favera report that BCL6 suppresses the expression of p53 to block DNA-damage-induced apoptosis in developing B cells.

In a survey of genes that rise and fall depending on levels of BCL6 expression, Phan and Dalla-Favera noticed that many were also targets of p53. This prompted them to investigate whether BCL6 might directly repress p53. This seemed reasonable as p53 is not expressed in cells that express high levels of BCL6, such as germinal-centre B cells. They showed that the p53 promoter did indeed contain a sequence that bound BCL6 protein, leading to downregulation of gene expression. Furthermore, inhibition of BCL6 with short interfering RNA in cultured B cells resulted in a 2–3-fold increase in p53 expression.

How might BCL6-mediated downregulation of p53 lead to lymphoma? The authors showed that treatment of cultured B cells with the DNA-damaging agent etoposide normally led to BCL6 downregulation and a resulting increase in p53 expression. B-cell lines engineered to constitutively express BCL6, as cancer cells do, could not upregulate p53, and were therefore resistant to etoposide-induced apoptosis.

In the normal B-cell lineage, BCL6 is highly expressed only in mature B cells within the germinal centre — the structure where immunoglobulin genes undergo genomic rearrangements such as somatic hypermutation and class-switch recombination. Phan and Dalla-Favera propose that in normal germinal-centre B cells, BCL6 upregulation suppresses p53-mediated responses as these cells undergo genome remodelling events required for B-cell development. BCL6 is normally then downregulated in response to large amounts of DNA damage, such as that induced by etoposide. The constitutive activation of this gene through mutation or chromosome translocation, however, causes p53-mediated responses to be permanently suppressed, leading to lymphomagenesis. These findings indicate that some types of lymphoma might be treated with reagents that target BCL6 and induce p53.

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References and links

ORIGINAL RESEARCH PAPER Phan, R. T. & Dalla-Favera, R. The *BCL6* proto-oncogene suppresses p53 expression in germinal-centre B cells. *Nature* **432**, 635–639 (2004)

WEB SITE

Ricardo Dalla-Favera's lab:
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TRIAL WATCH

Infiltrating influence

Patients with follicular lymphoma — a form of non-Hodgkin's lymphoma — can have indolent disease and survive more than 20 years, or aggressive disease and die within 1 year of diagnosis. There is no conclusive evidence that observation, chemotherapy, haematopoietic stem-cell transplantation or immunological therapy offers any significant survival advantage. Louis Staudt and colleagues have devised a survival predictor signature for follicular lymphoma and discovered that it is the profile of the tumour-infiltrating immune cells that is most useful to guide treatment decisions.

Follicular lymphomas arise from a germinal-centre B cell that has acquired a t(14;18) translocation that deregulates the anti-apoptotic protein BCL2, but, although further oncogenic changes do occur, it is unclear how they contribute to the progression of the disease. Louis Staudt and colleagues analysed fresh-frozen tumour-biopsy specimens from 191 untreated patients who had been diagnosed with follicular lymphoma 1974–2001 at institutes in the United States and Europe. These patients had subsequently received a range of treatments and had a median follow-up of 6.6 years. The biopsy specimens were divided into a training set and a test set.

Using a method called survival signature analysis, the authors used the Cox proportional hazards model to identify gene-expression signatures in the training set that correlated with survival. Ten clusters of coordinately regulated genes were observed in the training sets and the expression levels of the component genes within each signature were averaged. The authors then evaluated different combinations of these signature averages for their ability to predict survival, and found a combination of two particular signatures to be highly predictive of survival in both the training and test sets. Each unit increase in the survival-predictor score was associated with an increase in the relative risk of death — patients in the poorest survival quartile survived for a median of 3.9 years, and patients in the most favourable survival quartile survived 13.6 years.

The first signature, called immune response 1, includes T-cell markers (such as *CD7*, *CD8B1*, *STAT4*, *ITK* and *LEF1*) and macrophage markers (such as *ACTN*1 and *TNFSF13B*). Many other standard T-cell genes, such as *CD2* and *CD4*, were not associated with survival. The second signature, called immune response 2, includes genes expressed on macrophages and/or dendritic cells (such as *TLR5*, *FCGR1A*, *SEPT10*, *LGMN* and *C3AR1*). Surprisingly, it was the CD19-negative non-malignant cell population that highly expressed both of these signatures, whereas the CD19-positive malignant B cells did not. This finding highlights the importance of the immune system in this form of cancer.

The signatures could be used in conjunction with clinical prognostic indicators to identify the set of patients with indolent disease for whom observation would be the best course of action, and also the patients with the least favourable prognosis for whom enrolment into clinical trials of new treatments might be appropriate. The next step will be to evaluate these predictors of survival in a prospective trial.

ORIGINAL RESEARCH PAPER Dave, S. S. *et al.* Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N. Engl. J. Med.* **351**, 2159–2169 (2004)