THERAPEUTIC TARGETS

From microarray to mechanism

Why do patients with diffuse large B-cell lymphoma (DLBCL) — the most common form of non-Hodgkin's lymphoma — have such a variable response to chemotherapy? Eric Davis and colleagues now provide a rational basis for developing new types of therapies for the poor responders.

Microarray studies indicate that there are two types of DLBCL, one resembling resting, germinal-centre B cells (GC-DLBCL), the other, which responds poorly to standard chemotherapy, with characteristics of activated B cells (ABC-DLBCL). Analysis of these published results revealed that several genes in the NF-κB pathway are highly expressed in ABC-DLBCL, but not in GC-DLBCL. The same was true of cell lines derived from the two DLBCL types, and band-shift assays showed that high levels of NF-κB capable of binding its target sequences were present in ABC-DLBCL lines, but not in GC-DLBCL lines.

NF-κB is activated by degradation of its inhibitory subunit, IκB. The signal that sends IκB for destruction is phosphorylation by IκB kinase (IKK). Is this pathway operative in ABC-DLBCL? *In vitro* kinase asays revealed that IKK from ABC-DLBCL cell lines, but not from GC-DLBCL cell lines, was constitutively active and, when protein synthesis was blocked, levels of IκB in ABC-DLBCL cells plummeted, whereas IκB in GC-DLBCL cells was much more stable. So, NF-κB seems to be activated in ABC-DLBCL cells through the classical IKK pathway.

The authors then tried to block NF-κB signalling by introducing a 'super-repressor' mutant of IκB that cannot be phosphorylated by IKK. The super-repressor was toxic to ABC-DLBCL cells but had no effect on the survival of GC-DLBCL cells. So, ABC-DLBCL cells seem to rely on their constitutively active NF-κB signalling pathway for survival. Likewise, a dominant-negative mutant of IKKβ was also selectively toxic to ABC-DLBCL cells.

This mechanistic difference between the two types of DLBCL not only indicates why ABC-DLBCL might be more resistant to chemotherapy than the GC type, but also suggests a means of tackling that resistance. Drugs that block the NF-κB pathway are already in clinical trials, so it should not be long before these observations are put to the most important test of all — in DLBCL patients.

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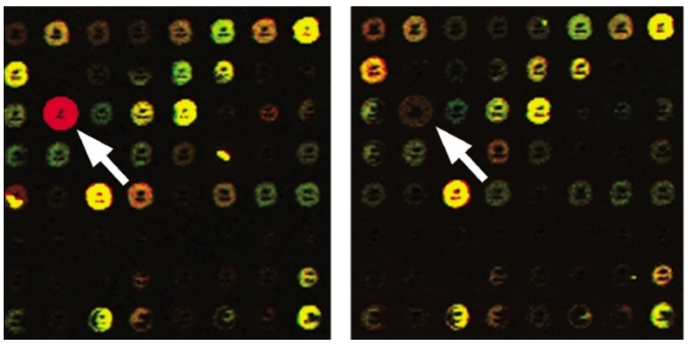
References and links

ORIGINAL RESEARCH PAPER Davis, R. E. *et al.* Constitutive NF-κB activity is required for survival of activated B-like diffuse large B-cell lymphoma cells. *J. Exp. Med.* **194**, 1861–1874 (2001)

FURTHER READING Alizadeh, A. A. *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* **403**, 503–511 (2000)



Microarray images from patients with germinal-centre B-like diffuse large B-cell lymphoma (left) versus activated B-like diffuse large B-cell lymphoma. Courtesy of Louis Staudt, National Cancer Institute, Bethesda, Maryland, USA.

TRIAL WATCH

Less tar is not necessarily safer

People who switch to low-tar or light cigarettes from regular cigarettes are likely to inhale the same amounts of cancer-causing toxins and remain at high risk for developing smoking-related cancers and other diseases. Millions of people smoke low-tar, mild or light cigarettes, believing that they are less harmful than other cigarettes. But in a recent report from the United States National Cancer Institute (NCI), entitled *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine*, experts conclude that changes in cigarette design and manufacturing over the past 50 years have not made smoking any safer.

Epidemiologists predicted in the late 1960s and 1970s that as more smokers used lower-yield products for longer periods of time, death rates from lung cancer would fall. Now, the NCI reports that choosing lower-yield cigarettes is not likely to reduce tar intake or disease risks. Furthermore, there is no evidence that switching to light or ultra-light cigarettes assists smokers in quitting. This might be because smokers who switch to low-tar or low-nicotine cigarettes from regular cigarettes compensate for the lower nicotine level by inhaling more deeply, taking larger or more frequent puffs, or increasing the number of cigarettes smoked per day. In 2001, about 172,000 Americans died of cancer because of their use of tobacco products (31% of all cancer deaths). This NCI report is the 13th volume in their 'Smoking and Tobacco Control Monograph Series', which began in 1991 to provide ongoing information about emerging public health issues in smoking.

WEB SITE
http://cancercontrol.cancer.gov/tcrb/nci_monographs/MONO13/MONO13.HTM

Revising renal cancer therapy

A combination of surgery and immunotherapy might provide a desperately needed means of prolonging survival of metastatic renal-cell cancer patients. Renal cancer has poor prognosis and resists chemotherapy, leading many physicians to advocate aggressive surgery. The value of removing the affected kidney, however, has been debated for many years. Several studies have reported that cytokine treatment can improve renal cancer outcome. The authors combined these approaches by treating metastatic renal-cell cancer patients with radical nephrectomy followed by therapy with the cytokine interferon-α-2b. They found that the median survival of 120 patients who received surgery followed by interferon-α-2b was 11.1 months, whereas the average survival time for 121 patients who received interferon-α-2b therapy alone was only 8.1 months.

Although the statistical significance of this study is debatable, the results do support those of a recent, smaller trial. The authors conclude that the combined treatment should be considered the standard of care in future Phase III trials.

ORIGINAL RESEARCH PAPER Flanagan, R. C. *et al*. Nephrectomy followed by interferon α-2b compared with interferon α 2b alone for metastatic renal-cell cancer. *N. Engl. J. Med*. **345**, 1655–1659 (2001)

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