news

Genes predict childhood leukemia outcome

Vida Foubister, vfoubister@optonline.net

By comparing the gene expression patterns of children with acute lymphoblastic leukemia who fail to respond to the conventional treatment to those who do, scientists at St Jude Children's Research Hospital have identified genes that could form the basis of a new prognostic indicator. Their insights also could lead to new therapies that reduce drug toxicities and increase response rates among affected children.

Common childhood cancer

Acute lymphoblastic leukemia (ALL) is a malignant disease caused by the abnormal growth and development of white blood cells in the bone marrow and blood (see Figure 1). It is the most common childhood cancer – about 3,000 children are diagnosed each year in the US alone – with the peak incidence from ages three to five.

The cure rate for children, defined as 10 years disease-free survival, has increased from less than 10% in the 1960s to nearly 80% today [1]. 'We have eight or nine antileukemic drugs that we usually give to every child based on their prognostic features at diagnosis,' explains William E. Evans, Director of St Jude Children's Research Hospital (http://www.stjude.org). These features include a child's age and leukocyte counts, as well as biological characteristics of their leukemia cells such as chromosome number and translocations [2].

But the current therapy's side effects and its failure to successfully treat 20% of affected children have researchers looking for new strategies. 'Typical side effects include infection associated with neutropenia or immunsupression, nausea and vomiting, oral or gastrointestinal mucositis, liver dysfunction, weight gain or loss, bone or joint abnormalities, not to mention hair loss and occasional neurologic dysfunction,' explains Ching-Hon Pui, Director of St Jude's Leukemia/Lymphoma Division.

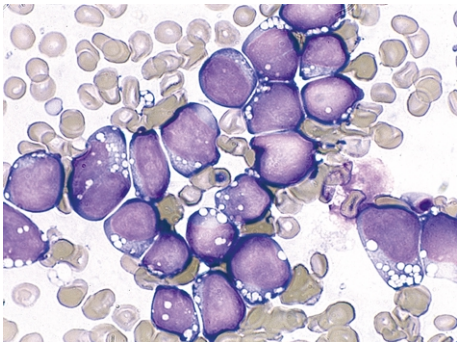

FIGURE 1.

Leukemic cells. Image courtesy of St Jude Biomedical Communications, Memphis, TE, USA.

Drug resistant gene patterns

Focusing on four widely used antileukemic drugs, St Jude researchers assessed single drug resistance gene expression patterns in ALL cells from 173 children treated at Sophia Children's Hospital in The Netherlands or Children's University Hospital in Germany and 98 children treated at St Jude [3]. Based on this study, they identified 124 differentially expressed genes, including 121 that had not previously been associated with resistance to the four tested drugs – prednisolone, vincristine, asparaginase and daunorubicin.

Building on these findings, they used a genome-wide approach to identify 45 genes differentially expressed in ALL cells from 129 European patients and 83 American patients with cross-resistance to all four drugs [2]. They also identified 139 genes related to a novel drug resistance, called discordant, in which leukemic cells are resistant to asparaginase but sensitive to vincristine. Patients with these two gene expression patterns had significantly poorer outcomes regardless of whether they were treated in Europe or the US – only 37% were found to be disease free five years after treatment.

Evans and his colleagues are now looking for novel therapeutic targets in these drug resistance pathways. The identified genes have biological functions that range from carbohydrate metabolism to glucose transport, protein metabolism and cell cycle regulation.

A prognostic indicator?

Although the microarray analysis used in the St Jude study is 'beyond the capabilities of standard clinical laboratories,' further elucidation of the critical genes involved in drug resistance could lead to the development of a hospital-based prognostic test, says Richard A. Larson, Professor of Medicine and Director of the Hematologic Malignancies Clinical Research Program at The University of Chicago. This, in turn, would help clinicians optimize treatment for each child.

'It's no longer the case that one shoe fits all,' Larson says. 'We need to adapt our treatment for the individual needs of a particular patient based not only upon their ability to tolerate the treatment but perhaps more importantly on any predictive information as to how resistant or how sensitive their leukemia may be to a drug or a combination of drugs.'

References

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