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Classifying lymphomas

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Abstract

DNA microarray analysis has been used for the first time to define clinically relevant subtypes of lymphoma.

Significance and context

Definition of distinct subclasses of cancer is important for improved understanding of the disease and of the differences in the response of patients to treatment. Such classifications initially relied on morphological and histological features of the cancer. The classification of human lymphomas, for example, dates back to morphological observations made by Thomas Hodgkin in 1832. Molecular analysis now provides additional criteria for distinguishing tumor subtypes of clinical relevance. DNA microarray technology enables the simultaneous, genome-wide analysis of gene expression in multiple tumor samples and the detection of patterns in the gene expression profiles. Non-Hodgkin's lymphoma is divided on morphological grounds into several subtypes, of which diffuse large B-cell lymphoma (DLBCL) is the most common. Cases of DLBCL are clinically heterogeneous and less than half of patients experience durable remission. However, it has not been possible to predict a patient's risk profile on the basis of clinical parameters or morphological criteria. Alizadeh *et al*. use gene expression profiling of DLBCL to address three issues: first, the generation of a molecular portrait of B-cell malignancy; second, the identification of distinct novel subtypes; and third, a characterization of B-cell physiology.

Key results

Gene expression profiles for 96 different samples of malignant and normal lymphocytes were examined using 128 DNA microarrays and 1.8 million expression measurements. Sophisticated hierarchical clustering algorithms were used to group samples into clusters with similar expression profiles, and a gene expression 'signature' was defined for each cluster. This analysis could distinguish DLBCL from other lymphocyte malignancies. DLBCL is known to proliferate rapidly and DLBCL samples displayed high expression of genes in the "proliferation signature" cluster. Further analysis divided DLBCL into two subgroups, germinal center (GC) B-like DLBCL and activated B-like DLBCL. These subgroups probably derive from populations at different stages of B-cell differentiation. The GC B-like DLBCL signature genes were not expressed in activated peripheral blood B cells. Conversely,

genes expressed in activated B-like DLBCL were not expressed by normal germinal center B cells. The expression pattern of the activated B-like DLBCL was similar, but not identical, to the signature of activated peripheral B cells. Finally, these two DLBCL subgroups distinguished two sets of patients. GC B-like DLBCL patients showed distinctly better overall survival; 76% were alive after 5 years, compared with only 16% of patients with activated B-like DLBCL.

Methodological innovations

Alizadeh *et al*.have designed the Lymphochip, a specialized microarray containing 17,856 cDNA clones. These include genes specifically associated with lymphocyte biology, immunology and cancer. Sixty-eight per cent of the clones were selected from a germinal center B-cell library. The rest come from other lymphomas, or are genes known to be involved in cancer or genes whose expression changes on lymphocyte activation. The entire data set of cDNAs is listed in the Web supplement to*Nature* **403**:503-511.

Links

The Lymphoma/leukemia molecular profiling project website maintained by Alizadeh *et al*. has details of many aspects of this study.

Conclusions

Alizadeh *et al.* show the power of gene expression profiling in the analysis of B-cell lymphomas. The authors suggest that the two groups - GC B-like DLBCL and activated B-like DLBCL - could be regarded as two distinct diseases. Similar analysis may allow the definition of further subgroups. Such an approach is likely to make a significant contribution to cancer diagnosis and to the development of targeted therapies.

Reporter's comments

Analyzing the expression of thousands of genes at a time is a powerful methodology for gaining insights into cancer signatures and clinically relevant cancer subclasses. As the number of tumor samples increases, it will be possible to reduce the number of genes in a signature to a core set that

defines each malignancy. Such information will be critical in the design and interpretation of cancer drug trials.

Table of links

Nature

Web supplement to *Nature* **403**:503-511

Lymphoma/leukemia molecular profiling project

References

1. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, et al: Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000, 403: 503-511. 0028-0836