cDNA Microarrays and Cutaneous Oncology

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Classification and Prediction of Survival in Patients With the Leukemic Phase of Cutaneous T Cell Lymphoma


We have used cDNA arrays to investigate gene expression patterns in peripheral blood mononuclear cells from patients with leukemic forms of cutaneous T cell lymphoma, primarily Sézary syndrome (SS). When expression data for patients with high blood tumor burden (Sezary cells >60% of the lymphocytes) and healthy controls are compared by Student's t test, at P<.01, we find 385 genes to be differentially expressed. Highly overexpressed genes include Th2 cells-specific transcription factors Gata-3 and Jun B, as well as integrin beta1, proteoglycan 2, the RhoB oncogene, and dual specificity phosphatase 1. Highly underexpressed genes include CD26, Stat-4, and the IL-1 receptors. Message for plastin-T, not normally expressed in lymphoid tissue, is detected only in patient samples and may provide a new marker for diagnosis. Using penalized discriminant analysis, we have identified a panel of eight genes that can distinguish SS in patients with as few as 5% circulating tumor cells. This suggests that, even in early disease, Sézary cells produce chemokines and cytokines that induce an expression profile in the peripheral blood distinctive to SS. Finally, we show that using 10 genes, we can identify a class of patients who will succumb within six months of sampling regardless of their tumor burden.

COMMENT

This article by Kari et al from L. C. Showe's research group at the Wistar Institute is emblematic of a new era in the analysis of cutaneous T-cell lymphoma (CTCL). Analysis of complementary DNA (cDNA) arrays determined the patterns of genes expressed by circulating leukocytes from patients with leukemic CTCL. Patients with CTCL showed differential expression of genes, including many that were overexpressed and others that were underexpressed.

From a biological standpoint, the expression of several genes was expected, such as high levels of transcription factors related to type 2 T helper cells and low levels of antigens like CD26 that are usually not expressed by Sézary cells. The differential gene patterns might lead to new insights into the pathogenesis of Sézary syndrome (SS) or provide novel means of diagnosis. For example, plastin-T is an actin-associated protein expressed in many cases of SS but not by normal T cells. Antibodies against this marker might be useful additions to existing antibody panels used in the diagnosis of CTCL.

Interestingly, panels of fewer than 10 genes can be used to discriminate between CTCL and controls with a high degree of sensitivity and specificity, even when there are as few as 5% circulating tumor cells. This implies that a relatively small proportion of tumor cells is able to produce factors that induce CTCL-specific patterns of gene expression by other peripheral blood leukocytes. Furthermore, small panels of genes were also able to identify those patients with a poor prognosis who died within 6 months.

In a related article by Tracey et al,1 cDNA arrays with a panel of 6 genes were used to discriminate, with a very high degree of sensitivity and specificity, between skin lesions of mycosis fungoides and inflammatory dermatoses. Many of the relevant genes in this study belonged to the tumor necrosis factor signaling pathway. Interestingly, this study showed up-regulation of STAT4 in mycosis fungoides, which contrasts with its down-regulation in SS. This difference might be due to an inherent difference between mycosis fungoides and SS tumor cells or between the cutaneous and peripheral blood microenvironments. cDNA arrays identified differences in gene expression associated with resistance to interferon alfa.2 The gene MAL, which was highly overexpressed by resistant cells, was found to be expressed by tumor cells among patients treated with interferon alfa and/or photochemotherapy and was associated with a longer time to complete remission.

Although all these findings must be confirmed by other observers, it appears that cDNA arrays of suspected CTCL will have useful clinical applications, including diagnosis, staging, monitoring disease activity, determining prognosis, and predicting response to various therapies. In the future, instead of obtaining biopsy specimens for routine histopathologic analysis, clinicians might obtain samples for cDNA array analysis to determine the characteristics of lesional T cells and the capabilities of the patient's immune system. This information may establish the diagnosis of CTCL, select the most appropriate therapies, and predict the patient's overall clinical outcome. The potential predictive power of cDNA array analysis makes it important for dermatologists to keep abreast of developments in this fascinating field.

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REFERENCES
