Molecular Signatures of Lung Cancer — Toward Personalized Therapy
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Lung cancer is the deadliest cancer in the world. Relapses are frequent after primary and adjuvant therapy and often evolve into lethal metastatic disease. Currently, lung-cancer staging rests on histopathological and clinical criteria that have only limited power to predict relapse and survival. A major effort to improve the control of lung cancer entails the use of molecular profiling to characterize tumors and provide accurate predictions of the outcome after standard or novel treatments.

Such molecular studies of lung tumors began with single or relatively small groups of potential prognostic markers and have progressed to microarray analyses of thousands of genes in large numbers of tissue samples. In this issue of the Journal, Chen et al. report on a study of gene-expression profiling in the most common lung cancer, non–small-cell lung cancer. They first studied a DNA microarray of 672 invasion-associated genes, which they had previously identified, in frozen specimens obtained from a series of 125 patients in Taiwan with surgically resected non–small-cell lung cancer. They first studied a DNA microarray of 672 invasion-associated genes, which they had previously identified, in frozen specimens obtained from a series of 125 patients in Taiwan with surgically resected non–small-cell lung cancer. The specimens represented a mixture of tumor types and stages and were randomly divided into a training set and a test set. None of the patients had received adjuvant chemotherapy. Of the original 672 genes, Chen et al. identified 16 that correlated with increased (4) or decreased (12) survival. This work permitted them to develop a score that discriminated between patients at high risk for death or recurrence and those at low risk. Chen et al. then used a real-time reverse-transcriptase–polymerase chain reaction (RT-PCR) assay to confirm the microarray findings in a subgroup of 101 specimens. The RT-PCR method showed that surviv-

The median overall survival was twice as long in the low-risk group as in the high-risk group (40 months vs. 20 months), and there was even greater improvement in the median relapse-free survival in the low-risk group (29 months vs. 13 months). The clinical significance of these results was strengthened by the results of an independent validation involving 60 patients treated at the same hospital. The stage of non–small-cell lung cancer also predicted survival in all these analyses, but the five-gene signature was effective in predicting outcome within subgroups — for example, patients with stage I cancer (P=0.02). The signature was further verified in a set of published microarray data from 86 patients in a Western population. In summary, this five-gene signature was found to be an independent predictor of recurrence and overall survival in three groups of patients with non–small-cell lung cancer who were treated only with surgical resection of the tumor.

This study produced robust, promising results, but it also raises several questions. Given that tumors are heterogeneous and that the biopsy specimens used by Chen et al. were not microdissected, the analysis could have underestimated or overestimated the importance of invasion-related genes, which can vary in expression throughout a tumor. Furthermore, molecular epidemiologic, stromal, and vascular factors are critical to the metastatic process, and these elements were not specifically analyzed in this study. The statistical design can also influence
the selection of a signature, and the choice of the cutoff of expression levels surely influenced how the original 672 genes were selected. The relationship of the signature genes to metastasis may be contributory or possibly only associative, and for this reason, proteomics will probably be useful in evaluating this question of cause and effect.

The work of Chen et al. reflects the maturation of the first phase of lung-cancer genomics, which has been based on stored tissue and clinical charts. The field is now poised to begin its next phase — conducting prospective trials of adjuvant chemotherapy in patients with early lung cancer who are selected because they have a high risk of relapse or metastasis according to the molecular signature identified by Chen et al. or others.\textsuperscript{3,4} Such trials should be conducted to validate the molecular signatures further and to assess whether patients selected according to their signature for treatment will indeed benefit from standard adjuvant therapy. This next phase of cancer genomics has already begun in lymphoma\textsuperscript{5} and breast cancer,\textsuperscript{6} with retrospective data (for breast cancer) indicating that adjuvant treatment is beneficial in patients identified as being at high risk according to genomics.\textsuperscript{7}

Next, cancer genomics will expand into two areas: molecular profiles associated with response or resistance to particular standard or novel therapies and clinical trials based on molecular profiles that indicate a benefit from new or standard agents. Recent examples of molecular markers of resistance include expression of the excision repair cross-complementation group 1 gene (\textit{ERCC1}) (resistance to cisplatin-based adjuvant therapy) and \textit{ras} mutations (resistance to cisplatin-based therapy and epidermal growth factor receptor [\textit{EGFR}] tyrosine kinase inhibitors).\textsuperscript{8-10} Such research suggests that molecular signatures can guide the choice of treatment for primary and adjuvant therapy.

A number of important signaling pathways that are involved in carcinogenesis in the lung have now informed platforms for assessing biomarkers associated with sensitivity or resistance to various agents that target these pathways. In lung cancer, the best current examples consist of the \textit{EGFR} mutations and amplification that identify patients with non–small-cell lung cancer who respond preferentially to \textit{EGFR} tyrosine kinase inhibitors.\textsuperscript{11,12} These signaling platforms link pre-clinical and clinical assessments of genomics (including global gene expression and epigenomics) and proteomic assessments of pathway activation.\textsuperscript{13} Given the recent approval by the Food and Drug Administration of the \textit{EGFR} inhibitor erlotinib (November 2004) and of the angiogenesis inhibitor bevacizumab (October 2006) for lung cancer, it is now crucial to create molecular tools that can predict the response of cancers to single agents or combination chemotherapies, in order to guide the development of new drugs or improve routine clinical care. These prognostic sig-

\begin{itemize}
  \item Phase 1: Genomic signatures
    Stored specimens plus clinical data
  \item Phase 2: Validation
    Prospective trials
  \item Phase 3: Expansion of genomic signatures
    Preclinical and clinical studies
  \item Phase 4: Personalized therapy
    Algorithm
    Clinical characteristics
    Molecular imaging
    Proteomics
    Genomics
\end{itemize}

\textbf{Figure 1. Development of Personalized Drugs for Lung Cancer, from Identification of Genomic Signatures to Prospective Trials of Personalized Therapy.}
natures can consist of new genes or include genes already established during earlier genomic testing. The signature reported by Chen et al., for example, includes ERBB3, a gene associated with sensitivity to EGFR tyrosine kinase inhibitors.\(^\text{14}\)

This new phase of target profiling and agent-specific profiling will probably require an algorithm that would include genomic, proteomic, clinical, and imaging factors (Fig. 1). The profiles, we predict, will be used for the development of novel drugs. Patients with early-stage cancers will be assigned to particular drugs on the basis of the molecular characteristics of the tumors. Then the development of drugs for the treatment of lung cancer will be focused on personalized therapy.

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