Editor's LETTER

ACS chemical biology

Lung Cancer — Genomics and Personalized Medicine

Cancer results from the accumulation of mutations and comprises over 100 diseases. Lung cancer, which causes more deaths than any other type of cancer, is a global health concern. Tobacco smoking is the leading risk factor for lung cancer, with smokers approximately 20 times more likely to develop the disease than nonsmokers. To date, scientists have identified more than 60 carcinogens in tobacco smoke that chemically modify DNA by forming bulky adducts at purine bases (*1*).

Most clinical cases of lung cancer are categorized into two subtypes based on histopathology: non-small-cell carcinoma (NSCLC) and small-cell carcinoma (SCLC). Currently, the long-term survival rates for patients diagnosed with either subtype of cancer are generally poor. Recent interdisciplinary studies that shed light on the prospect of "personalized" therapeutics and on the genomic underpinnings of lung cancer are reasons for cautious optimism (*1*, *2*).

Since lung cancer is essentially a genetic disease, it is useful to know how many genes are altered in solid tumors associated with the disease. Oncogenes such as those encoding members of the Ras family of proteins in the receptor tyrosine kinase pathway are activated by mutations that cause increased expression (*3*). These can result from gene amplifications, translocations, and specific point mutations. Conversely, tumor suppressor genes such as *TP53* (which encodes the p53 tumor suppressor protein) are inactivated by insertions or deletions, specific point mutations, or epigenetic silencing (*3*). Cataloging the complete set of oncogenes and tumor suppressors for a cancer will not be a trivial task, partially because disease progression does not occur identically in every patient.

On the bright side, recent advances in massively parallel sequencing technologies now make it possible to sequence whole genomes, exomes, and transcriptomes rapidly and cost-effectively. As a result, new cancer genomes are being sequenced at an astonishing rate. With new global initiatives, thousands of other cancer genomes from specific cell lines and tumors will be sequenced within the next few years, and as more cancer genomes are sequenced, it will be possible to identify new genes and key mutations (*4*).

Earlier this year, a landmark research article provided the first glimpse into the genome of lung cancer (*1*). Pleasance *et al.* sequenced the genome of an SCLC cell line and found 22,910 point mutations (of which only 134 were in coding exons), 334 copy-number alterations, and 58 genomic rearrangements. By examining these mutations, the researchers confirmed purines as the main target of compounds in tobacco smoke. A prediction in the study (based on the assumption that most mutations in a clone of lung cancer cells derive from chemicals in tobacco smoke) is that one mutation occurs for every 15 cigarettes smoked during the lifetime of these cells.

Studying cell lines is important but does not paint the complete picture. Until very recently, it had not been possible to identify the entire range of mutations in solid tumors. In May, Lee *et al.* described the sequence of an NSCLC primary tumor compared against the sequence of normal adjacent tissue (*2*). Diversity in the broad types of genetic alterations was observed in this study as well. However, when compared to the SCLC cell line genome,

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over twice as many total mutations (>50,000) were found in NSCLC tumors. This variation is not surprising given the difference in source subtype and the fact that solid tumors are more heterogeneous than cell lines.

Where do we go from here? A major challenge in cancer genomics is in identifying which of the genetic changes in coding regions are "driver" mutations that influence cancer progression and which are "passenger" mutations that are not causally connected. Another challenge is identifying mutations in noncoding regions that influence the expression of cancer-associated genes. In addition, epigenetic modifications and mutations to the mitochondrial genome need to be examined. Finally, as recent studies have shown, molecular characterization of lung cancer tumors will continue to be difficult due to the heterogeneity of the constituent cells.

The molecular targets of many early cancer drugs were not known. Today, therapies geared toward specific molecular targets are often hindered by disease heterogeneity. At the recently concluded general meeting of the American Association for Cancer Research, there was excitement surrounding the potential for using therapies personalized to individual lung cancer patients (*5*). Edward Kim at the University of Texas M.D. Anderson Cancer Center presented data from a phase-II clinical trial dubbed Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE). Roughly 250 patients with advanced NSCLC participated in the BATTLE trials. Briefly, biomarker groups for tumor-associated molecular signatures were used to sort patients into four cohorts; an additional cohort contained patients that could not be grouped by any biomarker. Patients were randomized and given one of four cancer therapies. After the initial randomization, the therapy was adapted on the basis of observed response to treatment. Interestingly, matching a biomarker to a therapeutic target on an ongoing basis resulted in an increase in survival of roughly 3−4 months compared to control. Although still too preliminary for use in the clinic, this trial underscores the need to characterize cancers on the basis of not only histopathology but also molecular targets and pathways.

What role will chemical biology play in cancer research in light of these exciting findings? The themes emerging from recent research on lung cancer can be extrapolated to other types of cancer. Increasingly, analyses of sequenced genomes in the search for key mutations will be automated. However, chemical biology approaches will be crucial in the identification and functional characterization of key players and pathways.

Chemical biology will also be vital in personalizing medicine, since successful implementation of clinical trials will depend on the identification of molecular targets and suitable therapeutics. There have been some spectacular success stories in cancer drug discovery, but few drugs entering clinical trials ever make it to market. Last year was not particularly great either: only four drugs received FDA approval for cancer therapy.

Given the difficulty in treating advanced stages of cancer, early detection will continue to play an essential role in disease management. Toward this goal, chemical biology will likely assist in the development of small molecule probes and new detection platforms.

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