Cancer genomics and its application toward personalized medicine

Yusuke Nakamura, M.D., Ph.D.
Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

In spite of recent progress in understanding the molecular genetics and biology of cancer, a large number of patients still suffer from side effects of anti-cancer drug therapy without experiencing any positive effects. More than a million of patients with advanced cancer worldwide die each year, of whom a significant proportion had been treated with radiation and/or chemotherapy. In view of the frequent ineffectiveness of these treatments, various approaches have been attempted to permit prediction of sensitivity or resistance to adjuvant therapy. A number of molecules, including multi-drug resistant genes, have been proposed as predictive markers, but so far none of them has proven to be clinically applicable.

Since the properties of cancer cells can vary enormously from one patient to another, it is not possible to characterize individual tumors by means of a single, or even several, molecular markers. In the past it was cumbersome and impractical to examine expression profiles of multiple genes, but the development of sophisticated microarray technology has enabled us to analyze thousands of them in a single experiment. As the properties of cancer cells are likely to reflect functions of all gene products expressed in cancer cells of a given patient, the set of genes whose expression is altered in that person’s tumor may represent significant determinants for his or her response to anti-cancer drugs. Therefore, we hypothesized that identification of dozens or hundreds of such genes might permit us to establish a novel diagnostic approach for personalized treatment of each cancer patient.

We applied cDNA microarrays representing nearly 27,000 genes to clarify properties of cancer cells that included cell lines, xenografts as well as clinical materials. A comparison of expression profiles of nearly 100 xenograft materials and their in vivo sensitivity to 9 anti-cancer drugs disclosed a set of genes that were likely to correlated with chemosensitivity. In addition, we also analyzed expression of 9216 genes in 20 esophageal-cancer tissues from surgical patients who were treated postoperatively with the same adjuvant chemotherapy, and classified the patients according to the duration of survival after surgery: $>30$ months (group 1: 8 cases), 12-24 months (group 2: 6 cases), $<12$ months (group 3: 6 cases). By comparing expression profiles of primary cancer tissues, we developed a "drug response score (DRS) " on the basis of differential expression of these 52 genes and found a significant correlation between DRS and individual patients’ prognoses. Validation by additional 4 patients (test case) has also supported that DRS correctly predicts the prognosis of those patients. Our results indicated that this scoring system, based on microarray analysis of selected genes, is likely to have great potential for predicting the response of individual cancer patients to chemotherapy.