EDITORIAL

Drug sensitivity testing for personalized lung cancer therapy

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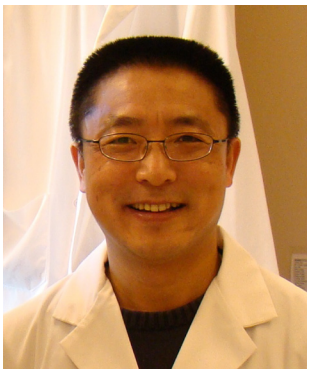

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Lung cancer is a biologically diverse disease. Non-small cell lung cancer (NSCLC), which represents about 80% of all lung cancer, is the leading worldwide cause of cancer-related death. NSCLC consists of adenocarcinoma, squamous cell carcinoma and large cell carcinoma (1). There are a number of conventional chemotherapeutic regimens available for NSCLC that, due to the heterogeneity of the disease at pathological, cellular and molecular levels, do not have the same effectiveness in individual patients. Oncologists have to decide which of the conventional regimens would potentially be optimal for a particular patient. The selection is crucial since the currently available chemo drugs are quite toxic and the toxic side effects of an ineffective regimen could preclude use of additional chemotherapy (2). There is therefore a need for reliable and relatively rapid chemosensitivity screening of an individual patient's NSCLC, aimed at identifying the best regimen for personalized chemotherapy of the patient on the basis of the patient's tumor biology. Several chemosensitive tests have been developed based on resected NSCLCs from patients, including *in vitro* tests using short-term cell cultures (3) and *in vivo* tests using first-generation tissue xenografts in immuno-deficient mice (4). An important criterion for such assays is that the cancer cell cultures and xenografts closely resemble the original cancers, in particular with respect to features that have a role in the chemosensitivity of the malignancy, including tumor heterogeneity and micro-environment (5). While *in vitro* assays based on short term cultures of patients' cancer cells are useful, the cell cultures do not possess the tissue architecture of the original specimens and lack interaction of cancer cells with factors from the original environment (e.g., stroma). As well, the transfer of cancer cells from the patient to the highly artificial *in vitro* environment may lead to loss of cancer subpopulations with different chemosensitivities. As such, the in vitro models generally do not accurately represent the patients' cancers. More accurate preclinical models are thought to be provided by subrenal capsule xenografts of patients' cancer tissues in SCID mice, since especially the first-generation xenografts tend to retain the cellular heterogeneity, architectural and molecular characteristics of the original cancer. This appears to be mainly due to the use of cancer tissue preserving the original micro-environment (as distinct from enzyme-digested cells), and use of the renal graft site which offers an abundant supply of nutrients, hormones, growth factors and oxygen to the transplanted tissue (4).

In this issue of the *Journal of Thoracic Disease*, Higashiyama *et al.* (3) describe differences between the chemosensitivities of primary and paired recurrent metastatic NSCLC tissues from

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patients obtained with an *in vitro* collagen gel droplet embedded culture drug test (CD-DST). This test has been used for some time in their institute to assess the sensitivities to anticancer drugs of surgically resected specimens from primary NSCLC lesions; when the test was applied to aid the development of individualized chemotherapies for NSCLC patients suffering from postoperative recurrence, a predictability of 70% was obtained. NSCLC is known for intratumor heterogeneity (6) and their finding that the recurrent metastatic lung cancer tissues had significantly lower chemosensitivities than the paired primary cancer tissues raises the possibility that the in vitro method did not detect very small subpopulations of cancer cells in the primary tissues with low or no chemosensitivity that were able to survive the patients' treatments and led to recurrence of the malignancy. Efforts aimed at identifying such subpopulations could hopefully be established using molecular markers and gene expression profiling of primary NSCLC tissues in conjunction with the biological assay (7). In fact, increasing evidence suggests that genomics-based, molecular diagnostic profiling is becoming one of the critical tools for making personalized cancer therapy a reality (8-10). In summary, given the heterogeneity of patients' tumors at molecular and cellular levels, the difficulties in identifying/isolating the malignant cells, and differences between clinical and experimental environments and conditions, it is indeed challenging to devise a system that truly mimics a patient's response. To overcome the obstacles involved, the following should be kept in mind: (I) better appreciation of the clinical and biological characteristics of a patient's cancer; (II) more effective integration of molecular profile and biological functional assays of a patient's cancer *in vitro* and *in vivo*; and (III) incorporation of new technologies in an evidence-based fashion into the standard of care to personalize treatment and improve individual outcomes.

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