Preview

Moving toward precision medicine with lung cancer organoids

James Kim[1,2,4,*] and John D. Minna[1,2,3,4]
[1]Department of Internal Medicine, Division of Hematology-Oncology, University of Texas Southwestern, Dallas, TX 75208, USA
[2]Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern, Dallas, TX 75208, USA
[3]Department of Pharmacology, University of Texas Southwestern, Dallas, TX 75208, USA
[4]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern, Dallas, TX 75208, USA
*Correspondence: james.kim@utsouthwestern.edu
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In this issue of *Cell Reports Medicine,* Wang et al.[1] generated 160 human lung cancer organoids, primarily from malignant effusions, and tested their responses to clinically used drugs to determine whether the *ex vivo* organoid responses predicted patient responses.

The goal of "precision medicine" is to tailor the treatment of diseases to the individual. For individuals with lung cancer, current clinical practice involves histopathologic diagnosis, tumor staging, identification of targetable oncogene driver mutations (such as mutant EGFR), and PD-L1 expression levels as predictive biomarkers of small-molecule targeted therapies and anti-PD-1/PD-L1 immune checkpoint blockade (ICB) therapies, respectively. However, the tumor biomarker-based approaches assume therapeutic responses *a priori* by generalizing the individual to the average individual—for example, that an individual with a lung adenocarcinoma (LUAD) with an oncogenic EGFR mutation will benefit from EGFR tyrosine kinase inhibitors (TKIs).

The advent of methods to grow tumor cells outside the body in tissue culture or as xenografts in immunodeficient mice raised the hope that the antitumor responses of drugs discovered in these *ex vivo* assays would be mirrored in affected individuals. However, this approach has yet to be integrated into clinical practice. With the development of methods for generating organoids, three-dimensional cultures of cancer specimens taken from the affected individual and grown in a basement membrane matrix, lung cancer organoids (LCOs) have come to the fore as an *ex vivo* system to determine therapy response phenotypes.[2,3] LCOs closely match the histopathology, mutational spectrum, and transcriptome of their parental tumors,[2,3] and so far, their *in vitro* responses appear to mirror what

were found in the individuals they were derived from.[4,5] Several methods for establishing LCOs have been reported, and the derived organoids can be used for drug response phenotype testing, including in high-throughput systems, a clear advantage over such tests in patient-derived xenograft (PDX) systems in mice.[2] Thus, LCOs offer a platform to test the drug sensitivities of an individual's cancer and select tailored therapies prior to its actual clinical implementation. However, there are no agreed upon standard methods and validation criteria for generating, testing, and evaluating drug responses of LCOs.[2,3] Success rates for LCO generation from primary and metastatic sites and different lung cancer histologies are highly variable. A significant issue is that LCOs derived from primary lung tumors often are overrun by organoids composed of normal airway epithelial elements.[6] Most importantly, there are only anecdotal data correlating LCO drug responses with affected individuals' tumor responses.

In this context, Wang et al.[1] set out to test the ability of LCOs to predict clinical efficacy of clinically used targeted therapy and chemotherapy agents in affected individuals. The authors generated a large biobank of 160 LCOs, 132 of which were from malignant serous effusions, the specimen source with a high, 82%, success rate. The LCOs were validated via morphologic and immunohistochemical analyses and, in a subset of 25 LCOs, genomic analyses. Tests of LCOs for drug sensitivity were performed using

drug panels that were tailored to each individual but broadly divided into osimertinib (an EGFR antagonist), chemotherapy, dual targeted therapy, and other targeted therapies. Analysis of 54 LCOs from 36 affected individuals whose clinical regimens matched those of the tested drug panels demonstrated very good to excellent concordance rates between the individual and organoid drug responses. Overall, the LCO-drug sensitivity tests (LCO-DSTs) demonstrated a sensitivity of 84%, specificity of 83%, and accuracy of 83% to predict clinical responses. Given the known high response rate of EGFR-mutant LUADs, the LCO-DST for the osimertinib group distinguished the IC_{50}s of the patient responder and progressive disease groups with an AUC 0.94 in receiver operator curve (ROC) analyses. By contrast, their data comparing organoid to affected indivuals' clinical responses for LUAD and small cell lung cancer (SCLC) to platinum-based doublet chemotherapy were anecdotal.

This study represents a solid step in the development of personalized organoids for precision medicine by establishing new baseline metrics of LCOs for therapeutic sensitivities and predictions of response. Larger, prospective clinial trials are needed that integrate standard tumor evaluation, molecular analyses, and LCO drug response phenotypes with individual tumor responses both for initial and second-line therapies. Encouragingly, the authors demonstrated that LCOs derived from lung cancers resistant to prior therapies were able to predict sensitivity to

combination targeted agents that were clinically utilized.

This reports also highlights limitations of this and prior studies of LCOs. The success rate of LCO generation is dramatically better for tumor samples from malignant effusions compared with primary or metastatic solid tumor sites. While only ∼16% of individuals with non-small cell lung cancer (NSCLC) will develop malignant effusions, this still represents a large number of individuals (∼42,000 new affected individuals a year in the United States).[7] Thus, we need improved methods to generate LCOs from solid tumor specimens, particularly from primary and metastatic tumors at the time of diagnosis or surgical resection, and methods to obtain tumor-containing organoids with minimal contamination from normal epithelial cells.[8] This study also raised the question about tumor heterogeneity in drug responses. Wang noted that both morphologic differences between the LCOs derived from a pleural effusion and metastatic lymph node from the same affected individual and that lymph node-derived LCOs were more sensitive to targeted agents than effusion-derived LCOs, suggesting the existence of intermetastatic tumor heterogeneity. Thus, whether LCOs from one site can accurately predict clinical responses at all tumor sites will need to be investigated further. The current and most recent studies focused on organoid/clinical correlations for targeted therapies. But platinum chemotherapies, in combination with taxanes, pemetrexed, gemcitabine, or etoposide, are still backbones for lung cancer therapy. Thus, correlations of LCOs and individuals' responses to chemotherapies are needed. Given that 50% of individuals with NSCLC receive radiation therapy at some time in their treatment course, radiation response phenotype data with clinical correlations are also needed. The most important new knowledge gap to fill is whether LCO cultures with appropriate tumor microenvironment and immune cells can predict individuals' responses to ICB therapy. A recent LCO model co-cultured with autologous T cells from peripheral blood[9] shows promise, but further validation is needed. The addition of other microenvironment components may further refine LCO models.

The study of Wang et al.[1] demonstrates the feasibility of using LCOs to tailor an affected individual's therapeutic regimens according to their cancer's *in vitro* responses. As part of this, it is crucial to note that LCOs can be "bio-banked," which will allow sharing of these resources between labs that, in turn, will provide a great experimental validation "force multiplier." Thus, the future is open for the development of additional methods, assays, and clinical correlative data for LCOs to eventually facilitate their entrance into routine clinical care.

DECLARATION OF INTERESTS

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