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PRECISION LUNG CANCER MODELING USING ORGANOIDS

Resume

Lung cancer organoids (LCOs) have emerged as advanced preclinical models that closely recapitulate the histological, genetic, and phenotypic features of patient tumors. By preserving tumor heterogeneity and enabling multi-omics integration, gene editing, and co-culture approaches, LCOs provide valuable insights into tumor biology, microenvironment interactions, and therapeutic responses. Although challenges such as low establishment efficiency remain, LCO-based precision modeling and biobanking represent powerful tools for translational lung cancer research and personalized therapy development.

Keywords: Lung cancer organoids (LCOs), patient-derived organoid, lung cancer,personalized therapy, organoid library, precision medicine.

Abstract

Lung cancer remains a major cause of cancer-related mortality, highlighting the need for more accurate preclinical models. Patient-derived lung cancer organoids (LCOs) have emerged as advanced three-dimensional systems that closely recapitulate the histological, genetic, and phenotypic features of primary tumors. LCO-based precision modeling preserves tumor heterogeneity, enables genotype–phenotype analysis through multi-omics integration, and supports the study of tumor–microenvironment interactions using gene editing and co-culture approaches. The establishment of LCO biobanks further enhances their value for translational research and personalized therapy development. Despite challenges such as low establishment efficiency, LCOs represent a powerful platform for advancing lung cancer research and precision medicine.

Introduction

Patient-derived LCOs mimic the genetic and histological characteristics of parental malignancies while retaining molecular and pathological characteristics seen in the clinic.1,7, LCOs and parental malignancies share chromosomal aberrations, copy number aberrations, and genetic alterations.2,3,4, 5. Crucially, a wide variety of recurring mutations found in sequencing studies are included in the established LCOs, offering useful biological models for cataloging driver gene alterations and creating tailored treatments.

LCOs keep the histological kinds of the initial malignancies, such as LUAD, LUSC, SCLC, and LCNEC, according to histopathological evaluations (Figure 2). These traits continue to exist in immune-deficient mice following xenografting, highlighting the durability of pathological morphogenesis.6, 7 Furthermore, LCOs include both molecular and histological subtypes in addition to major histological kinds.

For instance, transcription factor-based SCLC subtypes (ASCL1, NEUROD1, POU2F3, and YAP1 subtypes)27 and LUAD histological variations, including invasive mucinous adenocarcinoma, are retained in LCO organoids.Ten Neuroendocrine tumor organoids, such as models derived from SCLC, LCNEC, typical carcinoids, and atypical carcinoids28 that preserve subtype-specific molecular characteristics, have also been established in recent investigations. Understanding the relationships between genetic changes and the biological and morphological diversity of lung malignancies can be gained by preserving these (epi)genetic and histological subgroups. According to comparative genomic analysis, certain LCOs exhibit extra mutations that were not found in the corresponding parent tumors. These mutations could be the result of de novo culture-induced mutations or the emergence of uncommon subclones.7,8, 9, Prior research has shown that neutral clonal drift can gradually result in the dominance of single clones and the loss of intratumor heterogeneity, even though long-term-passaged LCOs often maintain the overall mutational spectrum and copy number variations of the parental tumors.31, 32 An accumulation of mutations and the growth of particular subclones during long-term culture were also noted in another investigation.17. These results suggest that clonal architecture in LCOs can change over time due to neutral drift and subclonal selection. Similar clonal dynamics have been seen in various cancer organoid systems, therefore they are not exclusive to LCOs.33 As a result, when interpreting results from organoids kept for varying culture times, researchers should be mindful of these limitations and, whenever feasible, evaluate clonal composition and genomic stability.31, 34

Through surgical resections or core needle biopsies of both intrapulmonary lesions and extrapulmonary metastases, we obtained NSCLC or macroscopically undetectable healthy lung tissue for organoid culturing. We obtained tissue from 46 adenocarcinomas, 4 squamous cell carcinomas (SCCs), 2 large cell neuroendocrine carcinomas, and 7 unspecified NSCLC samples. The bulk of the samples were stage IV adenocarcinomas, albeit they included a variety of tumor stages.

Materials and Methods

Tumor specimens were obtained from patients undergoing surgical resection or diagnostic biopsy at participating clinical centers. All sample collection was performed in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board (IRB). Written informed consent was obtained from all patients prior to tissue acquisition, permitting the use of samples for research, biobanking, and downstream experimental applications.

Fresh tumor tissues were transported in cold advanced DMEM/F12 medium supplemented with antibiotics and processed within 2–6 hours of collection. Samples were mechanically minced and enzymatically digested using collagenase and/or dispase to generate single cells or small multicellular clusters. Following filtration and centrifugation, cell suspensions were embedded in growth factor–reduced basement membrane extract (e.g., Matrigel) and plated as domes in multiwell plates.

Discussion

Precision lung cancer modeling using organoid technology represents a significant advancement in cancer research, bridging the gap between conventional in vitro models and patient-specific disease biology. Lung cancer organoids (LCOs) preserve key histopathological, genetic, and molecular characteristics of the original tumors, enabling a more faithful representation of tumor heterogeneity and therapeutic response than traditional two-dimensional cell cultures. This fidelity positions organoids as a powerful platform for studying tumor biology, drug sensitivity, and resistance mechanisms in a clinically relevant context.

One of the most compelling advantages of lung cancer organoids lies in their ability to capture inter- and intra-patient heterogeneity. Lung tumors are highly diverse, driven by complex genetic alterations, epigenetic changes, and microenvironmental influences. Organoids derived from individual patients can retain driver mutations such as *EGFR*, *KRAS*, *ALK*, and *TP53*, allowing functional evaluation of targeted therapies and combination treatments. This capability supports the growing paradigm of precision oncology, where therapeutic decisions are informed not only by genomic profiling but also by functional drug response data.

Despite these advantages, significant limitations remain. Most lung cancer organoids lack components of the tumor microenvironment, including immune cells, fibroblasts, vasculature, and extracellular matrix dynamics, all of which play critical roles in tumor progression and therapeutic response. This limitation is especially relevant for immunotherapy research, as current organoid systems cannot fully recapitulate immune–tumor interactions. Emerging co-culture systems and air–liquid interface models partially address this gap, but further optimization and standardization are required.

In conclusion,

Lung cancer organoids represent a transformative model system for precision cancer research. While challenges remain, continued technological refinement and interdisciplinary integration are likely to accelerate their translation from bench to bedside, improving therapeutic outcomes and advancing personalized medicine in lung cancer.

References

1.H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray,Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries,CA Cancer J. Clin., 71 (2021), pp. 209-249, 10.3322/caac.21660

2.C. Zheng, Y.H. Sun, X.L. Ye, H.Q. Chen, H.B. Ji, Establishment and characterization of primary lung cancer cell lines from Chinese population,Acta Pharmacol. Sin., 32 (2011), pp. 385-392,

3.M. Sugaya, M. Takenoyama, T. Osaki, M. Yasuda, A. Nagashima, K. Sugio, K. Yasumoto

4.Establishment of 15 cancer cell lines from patients with lung cancer and the potential tools for immunotherapy,Chest, 122 (2002), pp. 28228810.1378/chest.122.1.282

5.T. Sato, R.G. Vries, H.J. Snippert, M. van de Wetering, N. Barker, D.E. Stange, J.H. van Es, A. Abo, P. Kujala, P.J. Peters, H. Clevers
Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche, Nature, 459 (2009), pp. 262-265, 10.1038/nature07935

6.T. Sato, D.E. Stange, M. Ferrante, R.G.J. Vries, J.H. Van Es, S. Van den Brink, W.J. Van Houdt, A. Pronk, J. Van Gorp, P.D. Siersema, H. Clevers
Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium, Gastroenterology, 141 (2011), pp. 1762-177
7.K. Nanki, K. Toshimitsu, A. Takano, M. Fujii, M. Shimokawa, Y. Ohta, M. Matano, T. Seino, S. Nishikori, K. Ishikawa, *et al.*Divergent Routes toward Wnt and R-spondin Niche Independency during Human Gastric Carcinogenesis
Cell, 174 (2018), pp. 856-869.e17, 10.1016/j.cell.2018.07.027
8.T. Koga, J. Soh, A. Hamada, Y. Miyano, T. Fujino, K. Obata, S. Ohara, M. Nishino, M. Chiba, M. Shimoji, *et al.*
Clinical Relevance of Patient-Derived Organoid of Surgically Resected Lung Cancer as an In Vitro Model for Biomarker and Drug Testing
JTO Clin. Res. Rep., 4 (2023), Article 100554, 10.1016/j.jtocrr.2023.100554