European Journal of Clinical Oncology 2021, Vol. 04, Issue 03, 36-37 Mini Review

Lung Cancer Organoids

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Received: 05 -May, 2022, Manuscript No: ejco-22-75451; **Editor assigned:** 07-May-2022, PreQC No. ejco-22-75451 (PQ); **Reviewed:** 09-May-2022, QC No. ejco-22-75451(Q); **Revised**: 15-May-2022, Manuscript No: ejco-22-75451 (R); **Published:** 21-May-2022, doi: 10.35248/clinical-oncology.4(3).36-37

Abstract

Lung cancer morbidity and death have remained high in recent years despite the significant improvement in lung cancer research. As a result, a more in-depth understanding of the underlying molecular mechanisms of pathogenesis and the identification of novel, highly successful therapeutic techniques of therapy are soon to come in lung cancer research. Applying an effective and trustworthy preclinical model would be one of them and would be a crucial step throughout the entire procedure. Due to the absence of a tumour microenvironment or tumour heterogeneity, traditional 2D models utilised in lung cancer research, such as lung cancer cell lines and cell-derived xenograft models, cannot accurately represent the conditions of patients. Newly created 3D *in vitro* constructs called organoids more accurately mimic the structure, function, and genetics of human organs. Cancer organoids, particularly those produced from specific patients, can more closely resemble actual tumour tissues and so have a higher potential for generating advances in cancer research in the future. Here, we focus mostly on recent developments in the methods and uses of lung cancer organoids, which are still in the early stages of development but have enormous potential.

Keywords: Organoids • Lung cancer • 3D culture • Preclinical models

Introduction

The leading cause of cancer-related fatalities worldwide is lung cancer. Lung cancer affects almost 2.2 million people worldwide, and it claims 1.8 million lives annually. Small Cell Lung Cancer (SCLC), which accounts for 15% of occurrences, and Non-Small Cell Lung Cancer (NSCLC), which accounts for almost 85% of cases, are two separate histological subtypes of lung cancer. Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), and giant cell carcinoma are the three subtypes of NSCLC that can be identified. There is still a need for an efficient approach to early detection and precise treatment, despite significant advancements in lung cancer research and focused drug testing [1].

Currently, 2D models with lung cancer cell lines and Patient-Derived Tumour Xenografts are the most often utilised models in lung cancer research (PDTXs). Cancer cell lines, which are produced from the primary cancer tissues of patients, have made a significant contribution to cancer research for decades. However, because to the inherent mutability of cancer cells, even if cancer cell lines are widely available and inexpensive, they may experience genetic changes and may no longer maintain the original genetic heterogeneity across numerous passages. Another significant drawback is that, despite the tumour microenvironment appearing to play an increasingly significant role in the development and progression of cancer, cancer cell lines are unable to match the actual milieu of human cancer.

Compared to in vitro culture models, PDTXs, or surgically acquired primary clinical tumour tissues grafted into immunodeficient mice, offer the benefit of better simulating the original human tumour. PDTXs are frequently used in oncologic drug discovery and preclinical research because they maintain both intra and intertumoral heterogeneity. However, because they involve using animals and are expensive and time-consuming, they are not very effective. Additionally, interspecies compatibility and cellular component deficits in host models may affect stromal and immunological interactions [2]. New and more physiological human normal tissues and cancer models have recently been created because of the rapid advancement of 3D culture methods. Organoids can be produced from Induced Pluripotent Stem Cells (iPSCs) or adult stem cells that are unique to an organ, and then embedded in an appropriate Extracellular Matrix (ECM) such as Matrigel or basement membrane extract (ASCs). Cancer cells from various primary human tumour samples have also been utilised to create organoids that successfully recreate the tissue architecture of human cancer, which grows and organises into distinct tissue architecture in vivo [3]. In 2009, Sato et al. developed the first 3D epithelial organoids utilising a single intestinal stem cell expressing the G protein-coupled receptor 5 (Lgr5).

This served as the foundation for the development of numerous organoids in recent years, including those for the brain, lung, heart, breast, liver, stomach, colon, pancreas, salivary glands, and others. These so-called organoids could reflect more accurate and comprehensive structures and characteristics of human organs by simulating the *in vivo* niche environment. They could also be expanded over an extended period, cryopreserved, and maintain genetic and phenotypic stability, making them an improved model for cancer research. The inadequacy of cancer cell lines and PDTXs is thus addressed by tumour organoids, which could be produced more effectively from tumour tissue and multiplied under controlled conditions. This offers new hope in cancer model research due to their potential potent application in cell-cell interactions within the tumour microenvironment.

In 1946, Smith et al. coined the phrase "organoid," which means resembling an organ, to describe an instance of cystic teratoma. The term "organoids" now refers to 3D in vitro culture systems made from self-organizing stem cells that may imitate the structure, functionality, and genetics of organ tissues in vivo. Similar to lung tissue, lung organoids have advanced greatly in recent years and have been used to research a variety of pulmonary illnesses, including lung cancer. Embryonic and induced pluripotent stem cells as well as epithelial stem/progenitor cell types of the adult lung, such as basal cells, airway secretory club cells (formerly known as Clara cells), and Alveolar Type II cells (ATII), were the most common sources of lung organoids [4]. For the purpose of modelling cystic fibrosis, Wong et al. published the first in *vitro* directed differentiation process for Lung Organoids (LOs) made from Human Pluripotent Stem Cells (hPSCs) in 2012. Given that it has been shown that the activation of WNT and FGF signalling can jointly promote "morphogenesis in a dish," in which the 2D tissues self-organize into 3D spheroids made up of mesenchymal and polarised epithelial layers that separate from the adherent cell layer, while the inhibition of BMP/TGF-signalling can promote the development of tissue into a *SOX2*+ foregut lineage, Dye et al.

Squamous differentiation is a defining feature of LUSC, which mostly develops from the tracheal and upper airway epithelium. By immunostaining for cytokeratins 5 and 6, as well as the transcription factors *SRY-Box 2 (SOX2)* and *p63*, LUSC may be differentiated from LUAD. In LUSC, targeted mutations in LUAD are not very common. The tumour suppressor genes *TP53* (91%) and *CDKN2A* (19%) are the ones that are most frequently altered in LUSC.

Additionally, SOX2 overexpression and tumour suppressor gene deletion (*LKB1*, *PTEN*, or *CDKN2A*) can result in the development of LUSC differentiation, including the distal LUSC from secretory and ATII cells as well as the proximal LUSC from lung epithelial cells and basal cells.

As many cell types in the Tumour Microenvironment (TME) and their reciprocal interactions play critical roles in all stages of carcinogenesis and cancer progression, tumours have gradually come to be understood as organs [5]. The Tumour Microenvironment (TME) is made up of cancer cells, cancer stem cells, immune-inflammatory cells, Cancer-Associated Fibroblasts (CAFs), endothelial cells and pericytes, and the noncellular elements of the extracellular matrix, all of which are associated with cancer and is potential targets for cancer treatment. LCOs cocultured with cancer cells, cancer stromal cells, or immune cells thus serve as better models for researching cellular interplay inside the TME and reproducing key aspects of lung cancer.

Immunotherapy has recently become a popular method of cancer treatment, in addition to chemotherapy and targeted therapy. Immunotherapy advancements have consistently been a prominent issue in cancer research. LCOs offer a better way for further investigation of immune-oncology mechanisms and the creation of new combination therapy options for lung cancer since they are more appropriate *in vitro* models for examining cell interaction inside the TME [6, 7].

Although there are still some restrictions, such as the immaturity of this technology and the lack of use in direct clinical applications, these emerging studies in lung cancer organoids have demonstrated tremendous potential for all aspects of lung cancer learning, including basic and translational studies.

Conclusion

The success rate of cancer organoid establishment has significantly increased in recent years thanks to advancements in cultural technology. Even yet, different cancer types, people, and laboratories may use different culture media and passaging techniques. Additionally, although CRISPR/Cas9-mediated targeted gene editing in primary organoids demonstrated the potential to produce cancer organoids with appropriate genomic characteristics, it was limited to a small number of genes and, for the most part, was less effective. Additionally, organoid culture is still expensive, which restricts the use of this technology in cancer research on a larger scale.

The reason that the therapeutic uses of cancer organoids have not been widely extended is due to these barriers to cancer organoid research. Cancer organoids are a promising area for future fundamental and translational cancer studies, according to mounting evidence. We shouldn't limit ourselves to biological methods in order to increase the potential for organoid utilisation. Combining expertise from other disciplines, such as biochemistry and biophysics, is extremely beneficial to the development of organoid technology and should be the norm for future scientific research in all areas. For instance, our team has described a multidimensional biosensor system that included cellular impedance biosensors and 2D and 3D LUAD patient-derived cell models to test various anticancer medications and further direct LUAD individual treatment. Overall, improved standards, more advanced technologies and multidisciplinary intersections are mostly needed to further employ organoids in cancer research; only then can disease modelling, mechanism exploration, and drug testing with cancer organoids is more successful and credible.

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Cite this article: Vera, G.& Lisa, C. Lung Cancer Organoids. Eur J Clin Oncol, 2022, 4(3), 36-37