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3D CELL CULTURE SYSTEMS FOR ANTICANCER DRUG SCREENING

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ABSTRACT

Because three-dimensional (3D) cultures can more closely resemble tissue-like structures than monolayer cultures, they are gaining popularity. In cancer research, 3D cell models more closely resemble the architecture and features of natural tumors. Therefore, 3D cell cultures are more ideal and promising models, especially for in vitro drug screening to forecast efficacy in vivo. Various techniques have been devised to establish three-dimensional cell culture systems for scientific purposes. The most widely used 3D cell culture techniques for drug screening will be introduced and covered in this review. We'll also talk about how these systems might be used for anticancer medication screening.

1. INTRODUCTION

With 14 million new cases and 8.2 million deaths from the disease in 2012, cancer is one of the leading causes of death worldwide. The goal of many initiatives has been to develop novel and efficient cancer treatments. Anticancer medication screening is one of these tactics. Animal models have usually been used to assess standard screening. Nonetheless, certain findings indicate that human clinical outcomes are not always predicted by animal experiments, particularly when it comes to toxicity evaluations. Knight Furthermore, ethical considerations frequently lead to restrictions on the use of animals in research. Partying Given these concerns, using an in vitro model based on cells is a great way to reduce the number and necessity of animal experiments. Cell-based procedures were first established through 2D cell culture. Since 3D in vitro cancer models—especially spheroids and organoids—offer a more realistic depiction of tumor microenvironments than conventional 2D cell cultures, they are being utilized more and more for anticancer drug screening. These three-dimensional models aid in predicting medication resistance and identifying efficacious treatments, which may result in customized care. The most popular in vitro methods used in research labs to screen anticancer medications—dye exclusion, colorimetric, fluorometric, and luminometric assays—are discussed. This chapter provides an overview of the fundamentals, benefits, and drawbacks of the cell viability tests.

3D CELL CULTURE

Cell-based assays are essential for the screening of anticancer drugs. In the past, 2D cell culture was frequently employed in the search for new cancer drugs. But many medications that were shown to have potent anticancer effects in 2D cell culture models did not hold up in clinical trials Only 12 antineoplastic drugs were approved by the FDA following clinical testing in 2011, despite the fact that about 900 had passed through cell-based assay testing .Interest in 3D cultures' potential and vital role in cancer research has grown in recent years. By utilizing advanced three-dimensional multicellular tumor spheroid (MCTS) systems, tumor microenvironment, phenotype, and cellular heterogeneity are accurately modeled. 2015; Thoma et al. MCTS systems produce an oxygen gradient.

There have been reports that many antitumor drugs work less well on cancer cells grown in three dimensions than they do in two. (2000) Frankel et al.2015 saw Imamura et al.2012; Karlsson et al. The primary cause of this disparity is MCTS's architectural design. First off, anticancer agents are exposed to fewer cancer cells thanks to the three-dimensional structure of MCTS; this is because anticancer agents are more accessible to cells in monolayer culture. Lovitt, Carrie J. (2014). Second, according to Frankel et al. (2000), the ECM and tightly adhered cells in MCTS may restrict drug penetration. Additionally, a G0-dormant cell population that is extremely resistant to chemotherapy is produced by the hypoxic core. 2015; Imamura et al. Cells grown in 3D systems express different genes than cells grown in 2D monolayers, for example.

3D CELL CULTURE SYSTEMS PLATFORMS FOR ANTICANCER MEDICATION SCREENING:

Numerous studies have concentrated on the development and optimization of 3D cell culture technologies because of the benefits of 3D culture systems. A variety of 3D culture modes have been available up to this point, and anticancer drug screening has made use of them.

OVERLAY CULTURE IN LIQUID:

The most straightforward technique for 3D cell culture is liquid overlay culture (LOC). Enmon and others, 2001. In order to create models, a thin layer of inert substrates, such as agarose Friedrich et al., 2009, polyHEMA Friedrich et al., 2007 or Matrigel C. S. SHIN 2013, is applied to cell culture plates or flasks. LOC readily encourages 3D aggregates

or sph by inhibiting matrix deposition.

A BIOREACTOR:

Following the discovery of the crucial role that 3D cultures play in evaluating the chemical effects of anticancer drugs, scaling up screening from the laboratory to the industrial scale became imperative. Because bioreactors offered more production control and reproducibility, they were incorporated into the standard procedure for spheroid generation. Hosseinkhani and Ou, 2014. According to Breslin and O'Driscoll (2013), spheroids are typically created in bioreactors using a continuously moving fluid. According to S. Shin (2013), the primary methods of generating the dynamic culture condition are spinning (spinner flask) or stirring (NASA rotating wall vessel).W.F. McLimans created the modern glass spinner flask for the first time in 1957 (Mc et al., 1957). The suspension of cells was kept within flasks that had two arms and could be opened to exchange gases.

Applications in anticancer drug screening

Cell culture systems have long been a foundation for testing and comparing the cytotoxicity and pharmacodynamics of anticancer drug candidates. Even now, many results from 3D cell culture have consistently stressed the importance of these models in drug screening. Research by Jayme

L. Horning et al., published in 2008, indicated that 3D MCF7 cells were more resistant to many popular anticancer drugs (e.g. doxorubicin, paclitaxel and tamoxifen) compared with MCF7 cells cultured in monolayer. Using polymeric microparticle surfaces to create 3D tumors, they found that 2D MCF7 cells were significantly more sensitive to these drugs than 3D MCF7 cells, with a 12- to 23- fold disparity in the IC50 values. The study also showed that the sum of collagen in the 3D model was 2 times greater than that of 2D condition and the expression of many genes were different, possibly accounting for the difference in responses to the drugs Horning et al., 2008. Vesa Hongisto et al. suggested in their 2013 studies that 3D cell models can effectively replace traditional 2D cell monolayers and that with regard to screening of drug compounds, 3D models provide better comparability to clinical results. In their study, 102 compounds were tested on JIMT1 breast cancer cells. Results showed that JIMT1 cells were significantly more sensitive to 63 compounds when cultured on Matrigel as compared to 2D condition Hongisto et al., 2013. Using 96-well roundbottom ultra-low attachment plates to create 3D cancer tumors, Amy L. Howes et al. showed, from their studies in 2014, that 3D BT-474 cells were more

sensitive to lapatinib, gefitinib, vinblastine and vinorelbine than 3D MCF-10A cells. The authors also found that microtubule-targeting agents and epidermal growth factor receptor (EGFR) inhibitors are two classes of compounds to have selective effects on cancer cells in 3D culture Howes et al., 2014b. Work by Yukie Yoshii et al., published in 2016, on human colon cancer HCT116 cell line demonstrated that regorafenib was most effective on 3D HCT116- RFP cells among 8 drugs tested (capecitabine, bevacizumab, irinotecan, cetuximab, 5-fluorouracil (5- FU), panitumumab, oxaliplatin and regorafenib). Based on their 3D culture studies, the authors were able to demonstrate effective and non-effective drugs for colon cancer treatment Yoshii et al., 2016.

2. CONCLUSION

Anticancer drug screening is an important component in the fight against cancer. Several 3D cell culture systems have been developed as suitable platforms for drug screening and are serve as more reliable models for in vitro testing, compared to 2D, given that MCTS have greater structural similarity and cellular zone components to in vivo tumors. The 3D model systems should provide more accurate results for prediction of clinical outcome. Tremendous efforts have been made to establish various 3D cell culture systems. It is important for researchers to look carefully at the advantages and disadvantages of each to find the most suitable system for their studies. However, all the 3D systems can be utilized for cancer research, particularly for testing of new anticancer agents.

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