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3D tumor models for cancer drug discovery: Current status and outlook

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The history of cell culture spans more than a century, from the culture of the neural plate of a chick embryo by Wilhelm Roux in 1885 to the maintenance of tissue fragments *in vitro* for weeks by Ross Harrison in 1907 [1,2]. It was in 1951 that the now well-known HeLa cells became the first human cancer cell line to be cultured successfully, which was a major milestone in cancer cell culture and *in vitro* investigation of human cancer. New anti-cancer drugs have since been tested on two-dimensional (2D) cancer cell monolayers during preclinical screening studies. Although our knowledge of cancer cell microenvironment and heterogeneity has advanced greatly, the complexity of our *in vitro* tumour models has not improved proportionately. *In vitro* testing on 2D cell models may also have accounted for the high attrition rate of anti-cancer drugs being tested clinically; 95% of anti-cancer drugs in clinical trials tend to fail due to inefficacy and toxicity despite showing promise during preclinical testing [3]. This recognition of the limitations of 2D monolayer models has resulted in a recent surge in the development of three-dimensional (3D) tumour models for drug screening applications.

3D models in cancer research

Of the many three-dimensional tumour models currently under investigation, the most common are the tumour spheroids. These cell aggregates can be generated using a hanging drop technique, suspension/spinner flasks, ultra-low attachment plates, micro patterned plates, or a magnetic levitation technique where magnetic nanoparticle-encapsulated cells are made to 'levitate' and form spheroids using an external magnet [4,5]. 3D tumour models can also be prepared using microfluidics devices, by providing a scaffold/substrate/microbeads for cell attachment, or by encapsulation within materials like alginate, which offers better control over their sizes [6]. The 3D tumours were initially generated using a single cancer cell line (monocultures) but models involving co-cultures of different cell lines (e.g. cancer cells with stromal fibroblasts and macrophages) are now being explored. 3D tumour models being investigated today have thus evolved into complex structures comprising of multiple cell types from the tumour microenvironment and some models have micro vessels to represent the tumour vasculature. Preliminary investigation of these tumour models and comparison with conventional 2D cell monolayers have shown a marked difference in the way the cells respond to anti-cancer agents based on cell arrangement [7,8].

Future outlook

Despite the advances seen in recent years in the development of 3D tumour models, we still have a long way to go in terms of recapitulating a tumour and tumour microenvironment accurately in an *in vitro* setting. Most tumour models are able to mimic only certain aspects of a tumour environment and are thus not an accurate representation of tumour complexity and heterogeneity. Also, several of the reported tumour models are limited by inconsistent sizes which often results in inconsistent and unreproducible results during *in vitro* experiments due to batch-to-batch variations. Inability to support long-term cell growth, non-uniform cell attachment and lack of high throughput methods of tumour model formation are other limitations of existing 3D models [9]. There is therefore an urgent need for an *in vitro* tumour model with controllable physical and spatial parameters, which can represent the tumour microenvironment consistently and accurately, and provide reliable and reproducible data when used for *in vitro* drug testing. Comparison of cell responses with in vivo responses is pertinent in order to choose the most appropriate biomimetic model for future studies. Cost is another important factor to be considered while developing these 3D models. In fact, high cost and the time-consuming nature of in vivo studies are the reasons why 3D cell models are needed for preliminary pharmaceutical drug screening experiments. Therefore, a high-throughput, relatively inexpensive 3D cell model which is easy to develop, would have a higher chance of being adopted by researchers around the world for *in vitro* experiments.

This is an exciting time in cancer research; with new advances taking place frequently in cancer immunotherapy, gene editing and chemotherapy, there is a need for *in vitro* tumour models that can recapitulate the tumour environment relatively accurately for testing these new technologies and pharmaceutical drugs. The results generated using these models will help discard ineffective therapies during the initial stages of testing, while accurately identifying drugs with high therapeutic potential for further investigation. Millions of dollars are spent in developing, testing and validating anti-cancer agents and bringing them to clinical trials. Testing using *in vitro* 3D tumour models can potentially reduce the chances of pharmaceutical drug failure during clinical trials by accurately predicting clinical responses to drugs, so that therapeutically effective anti-cancer drugs can reach the patients without delay.

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