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Different Chemo-Sensitivity Used in Translational Viability

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Abstract

Although the in vitro analysis of cultured cell lines is associated with arti-facts related to effects attributed to a non-physiological environment and long-term passage in culture, it was shown that cancer cell lines retain most of the genomic features of the primary tumour. This has not yet been shown for proteomic features of cancer cell lines.

Keywords: Apoptosis; Drug testing; Drug sensitivity; Tumour environment; Xenograft; Pharmacological interventions

Introduction

The awareness of the importance of the tumour microenvironment and the three-dimensional aspects of solid tumours, in the response to anticancer therapy has initiated efforts to display these features in vitro more accurately. There are also several other important factors to take in regard to mimic the in vivo microenvironment of a tumour in vitro. For example, a whole field within cancer research is dedicated to the investigation of hypoxia, which is defined as inadequate oxygen supply to cells and tissues, in solid tumours and implications on anticancer treatment [1]. The oxygen concentration of 21%, used in most in vitro culture systems is not physiological in regard to the limited oxygen supply of cells within a solid tumour. Since it has been shown that the cellular signalling network, e.g. regulation of apoptosis is influenced by 3D cell organization and multicellular complexity, new cell culture models for a more realistic investigation of tumour cell behaviour ex vivo are urgently needed. To establish such models, it is necessary to maintain or reconstitute an environment which closely resembles the tumour in vivo. One of the first approaches of rebuilding the 3D microenvironment during in vitro cultivation and drug testing was the development of a culture model called Spheroids. In 1970, the first spheroid model was devised by Sutherland [2].

Methodology

Meanwhile, spheroids have been grown from a variety of normal and tumour cell lines and used in different assays, to study anticancer therapy efficiency as well as 3D cellular interactions. Single cell cultures were used to establish an organoid-like 3D model using different techniques. These different culture techniques include various artificial as well as natural ECM`s and mechanical methods to generate defined, roundly shaped cell clusters [3]. Matrices, such as agarose, collagen, gelatin or matrigel allow the establishment of culture systems with well-defined geometry, wherein the 3D structure affects interactions between cells. This usage of 3D matrices has been reported to show fruitful results in recapitulating tissue functions in 3D [4]. Besides various cancer cell lines, cell types like Madin–Darby canine kidney cells and fibroblasts, have also been monitored in 3D contexts and have provided valuable insight into the basic molecular mechanisms of polarity, adhesion, cell migration and response to anticancer therapy. Numerous studies have documented differences in cancer drug sensitivity between cells cultured in monolayers and those grown in 3D cultures. Previous studies have shown that certain drugs are more effective in 3D cell culture systems, although other drugs showed greater activity in the 2D cell culture systems [5]. These days, fewer than 100 human tumour cell lines have been reported to grow in spheroid cultures. Platforms based on tumour spheroids have been developed and are being used for analysis of individual chemo-sensitivity and secondary screening of potential new anticancer compounds. The application of spheroids in drug screenings has been reviewed by Friedrich and colleagues [6].

Discussion

However, it remains to be demonstrated comprehensively that chemo-sensitivity data derived from 3D cell cultures captures clinically relevant responses more precisely than standard 2D cultures. Furthermore, these systems cannot completely mimic the complex tissue architecture and the high degree of variability seen in individual tumours. It has been shown that signalling and metabolic pathways in cell lines have distinctly different expression patterns compared to tumour tissues [7]. Pathways in cell lines tended to be up-regulated compared to tumour tissue with exceptions in genes involved cell adhesion, ECM-receptor interaction and focal adhesion. As discussed before, spheroids are a good approximation to the in vivo tumour, but still lack the natural tumour environment, including the state of receptors and corresponding extracellular signalling between diverse cell types naturally being present in the tumour as shown in (Figure 1). Therefore, the development of in vitro organoid cell culture models was an essential step for translational research. First experiments were performed in 1967 by Matoska and Stricker, using tumour cubes of approximately 1 mm3 for in vitro culturing. Later, an in vitro histo-culture system, using a native-state collagen-sponge gel to support the three-dimensional growth of tumour tissue sections was developed, called the Histo-culture Drug-Response Assay [8]. Features of the histo-culture system include the maintenance of three-dimensional tissue architecture and the use of histological autoradiography or colorimetric assays as endpoints for determination of chemo-sensitivity. Ohie published a protocol on the Method of the HDRA. The reliability and utility of the HDRA were examined in several clinical studies for different tumour entities, e.g. oral squamous cell carcinoma, head and neck cancer, gastric cancer, colorectal cancer and ovarian cancer. Up to now, it has not been shown that the HDRA is also able to predict efficiency of targeted drugs such as small molecules and antibodies. The past years have seen unprecedented developments in the use of human

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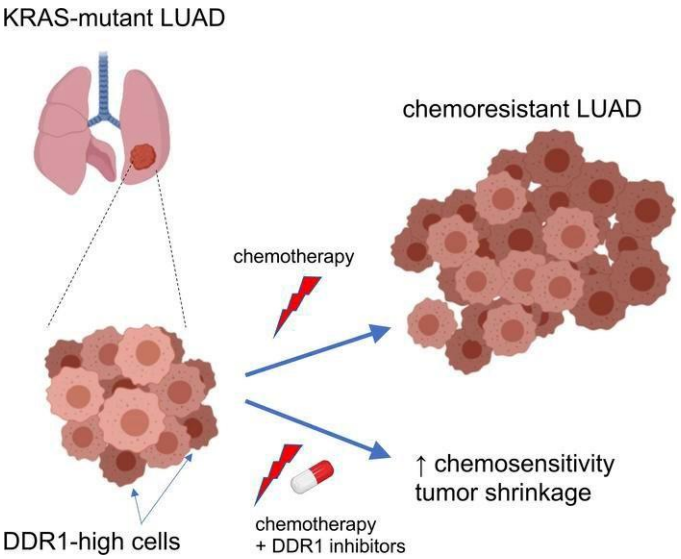

Figure 1: Inhibition in vivo chemo-sensitivity.

tissue surrogates in vitro [9]. Clevers developed a technique in which adult stem cells, originating from fresh tumour tissues, are embedded in a three-dimensional matrix and allowed to self-organize into epithelia of the respective organ of origin. The resulting organoids represent the physiology of native epithelia much better than traditional cell lines [10]. Mini-guts, for example, reproduce the epithelial architecture of small intestine and colon. If combined with genetic information and pharmacological profiles, such an organoids could aid in identifying markers that predict a patient's drug response similar to the Cancer Cell Line Encyclopedia. Parallel to the development of tissue microtomes enabling the preparation of thin slices of fresh tissue, precision cut cancer tissue slices from tumour tissue have become more popular as ex vivo systems. It has been shown, that cell viability of tissue slices was maintained in in vitro culture for at least 4 days [11]. After treatment with different compounds, slices can be fixed by immediate freezing or by formalin. Frozen slices can be used for several assays, e.g., functional drug effects on viability, apoptosis, proliferation and signal pathway analysis. Formalin-fixed slices can be utilized for immune-histo-chemical analysis of target expression, drug effects and cell–cell interactions. Furthermore, laser capture micro dissection can be applied, allowing the separation of different cellular compartments, for molecular analysis of pure cell populations. Viara and colleagues reported on a preclinical model of organotypic culture for pharmaco-dynamic profiling of human tumours. This model demonstrates the ability to detect pharmacological interventions ex vivo in a presevered original cancer microenvironment [12]. Due to the broad spectrum of molecular techniques that can be implemented, organoid cell culture models offer a unique opportunity to understand the complex basis of cellular responses to anticancer therapeutics of all groups, e.g. classical chemotherapeutics, small molecules and therapeutic antibodies. Despite the advantages of the models, difficulties in obtaining specimen and limited viability of these tissues in culture over time represent major obstacles [13]. The successful cultivation of tissue slices is also dependent on tumour entity, highly adapted culture conditions in terms of media supplements and other culture techniques. In the future, the use of miniaturized cell-based models that are specifically engineered to closely reflect in vivo behaviour can reduce costs and add efficiencies to drug development, but most importantly increase the accuracy of molecular prediction of response to anticancer therapy [14]. Currently existing in vitro cancer cell culture models, such as primary cell lines and organoid cultures are a solid basis for molecular drug testing, but they do not reflect the natural tumour environment in all facets. The final application of anticancer drugs takes place in the in vivo situation, in the patients [15]. Since it is unethical to use patients for preclinical research, xenograft cancer cell culture models were developed to facilitate drug testing in vivo and thus improve basic and translational research and prediction of individual response to chemotherapy. Cancer cell characteristics, such as chemo-sensitivity to anticancer chemotherapy, are strongly affected by several parameters in a physiological, in vivo, situation [16]. In contrast to in vitro cell culture models, xenograft models offer micro environmental conditions, e.g. tumour architecture, angiogenesis, metastasis close to the real patient. The injection of vital human cancer cells or even transplantation of human tumour fragments is therefore still essential to study cancer in an in vivo situation as shown in (Figure 2). Among the existing in vivo cell culture models, the mouse model is widely used. It bears the relative advantages of good availability, low space requirements, low cost, ease of handling and fast reproduction rate [17]. Mouse xenograft models are extensively being used to study individual response to anticancer therapy and drug development. Several studies on DNA and protein level were conducted in mice xenografts to understand and predict response to anticancer therapy. For example, gene expression signatures and plasma protein biomarker have been reported to predict efficiency of therapy ex vivo. But there are also multifaceted parameters affecting outcome when conducting xenograft experiments, e.g. site of implantation, growth properties and size of tumour at the time treatment is administered, agent formulation, scheduling, dose and the selected endpoint for assessing activity. A basic review on the mouse model in drug testing was published by Mattern L. and colleagues in 1988. The application of xenografts in drug testing has been reviewed elsewhere in detail. Despite the relatively comprehensive ability of mice models to mimic the clinical situation in patients, there are differences between mice and humans which might have an impact on the predictive value of this model. Mice and humans obviously differ largely in body size and lifespan. Although mice have a similar incidence of cancer at the end of the life cycle, they primarily develop cancers in mesenchymal tissues, e.g. lymphomas and sarcomas [18]. Most cancers in humans are of epithelial-origin and lead to carcinomas. Furthermore, the basal metabolic rate of mice is much higher, which results in increased generation of reactive oxygen species, other mutagens and

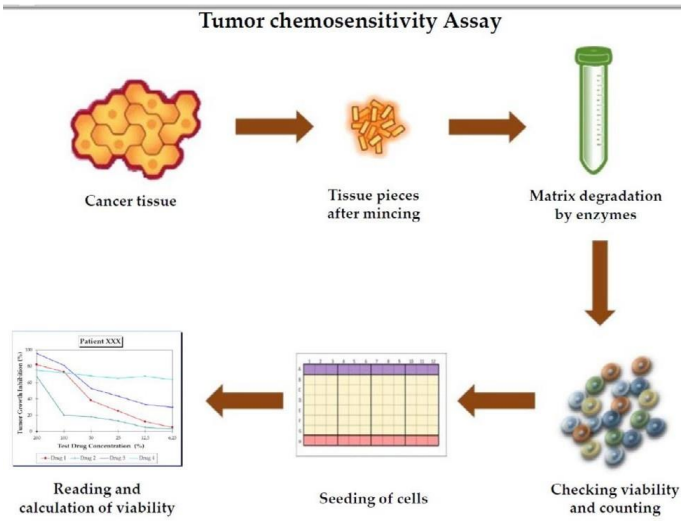

Figure 2: Tumour chemo-sensitivity.

also distinct metabolism of anticancer drugs in mice from humans. Xenografts may also fail to recapitulate immunological aspects of tumour-stroma interactions that are present in human patients. Cell signalling interactions between cancer cells and host stromal cells may not occur properly due to interspecies incompatibilities, e.g. interactions of ligands of one species with receptors of the other. Those incompatibilities may impact various characteristics of tumours, e.g. drug response and metastatic behaviour. A short overview of the challenges of selecting the 'right' in vivo oncology pharmacology model and improving the translation of these models to a clinical setting was summarized by Firestone B, 2010. Nonetheless, xenograft model are useful preclinical models [19]. The better these models are characterized on genome and proteome level and by implementing the learning experience while using these models, the more basic information on the individual response to anticancer therapy will be gained. First experiments to determine the individual chemo-sensitivity of tumour cells from cancer patients were made in the mid-1950s. At that time, techniques for chemo-sensitivity testing were developed on the basis of well-known parameters such as colony forming ability, growth inhibition or cell viability. In theory the overall effects of cytotoxicity are the sum of all specific cellular effects underlying multi-factorial mechanisms. Therefore, in vitro chemo-sensitivity testing can potentially predict response to anticancer therapy either by determination of the death of all cancer cells or at least by complete growth inhibition. Currently, chemo-sensitivity tests find wide application in basic and translational research. The measurement of drug effects on cell viability is integrated in basic research, for the detailed analysis of efficiency and mode of action of drug candidates, as well as in the clinical setting for the general determination of chemo-resistance of a patient's tumour. The measurement of cancer cell chemo-sensitivity to miscellaneous compounds with potential anticancer activity is the basis of most drug discovery programs.

Previous publications described various phases of the development of an in vitro anticancer drug screen, aimed at the identification of compounds showing selective growth inhibition or cytotoxicity towards particular cell or tumour types [20].

These screening programs require very robust, automated chemo-sensitivity assays for the measurement of drug effects on cancer cell viability or growth.

Conclusion

Therefore, many studies were performed comparing chemo-sensitivity assays in regard to their sensitivity, reproducibility, applicability to cancer cell lines of various origins and potential for adaption to high-throughput. In vitro chemo-sensitivity tests are, to some extent, applied in the clinical setting to determine chemo-resistance in a patients` tumour. This may help to guide individualized anticancer therapy, especially in second-line treatment where the guidelines for therapy are not always clearly defined.

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Conflict of Interest

None

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