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Malignancy Harder to Treat or Cure Cancer

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Abstract

The prediction of response to chemotherapy at the molecular level is currently mostly based on data derived from in vitro experiments. Besides studies in patient populations and xenograft models of tumors, cell cultures are the most commonly used in vitro systems for the analysis of cellular responses to drug treatment.

Keywords: Cellular responses; Cell lines; Extracellular matrices; Angiogenesis; Anticancer therapy; Artificial manipulation

Introduction

Various types of cell culture models exist. These models differ in their ability to reflect the in vivo situation, which is of great importance for further translation of results to the clinical setting. As a result of the gain in knowledge of cancer-specific signalling networks and metabolic pathways, it became obvious, that cell behaviour is strongly influenced by the microenvironment of the cell. These findings had great impact on the development of in vitro cell culture models and their use in drug discovery and translational research. 2D cell cultures are the oldest and widely used models in cancer research, comprising mainly clonal-secondary and infrequently primary cell lines [1,2]. Clonal-secondary cell lines are inexpensive in acquisition and easy to handle. Due to their ability to grow infinitely, they are well applicable in high-throughput screenings, suitable for genetic modification and good sources for preparations of cell components [3,4]. However, the preparation of cell lines from a tumour, results in loss of the 3D in vivo structure and in diversity of cell populations, thus these models only partly represent the origin tumour. Alongside the progress in laboratory technologies, the design of more and more extensive in vitro models became possible [5,6]. Based on first attempts to rebuild 3D tumour structures, using secondary cell lines and natural as well as artificial extracellular matrices, the techniques for the preparation of such models rapidly advanced [7,8]. Currently, the mixed culture of different cell types, the use of feeder layer cell lines and the induction of angiogenesis in these 3D cell culture systems are main improvements in this area of research. Nonetheless, these models represent artificial microenvironments and many features of an original tumour cannot yet be displayed. Complex models such as in vitro 3D-organoid cell cultures or xenografts currently best display the characteristics of an in vivo tumour. The cultivation of vital tumour tissue slices, for example, enables drug testing in a natural tumour environment and has the capability to reveal tissue composition dependent cellular responses to anticancer therapy. Since the introduction of chemotherapy for cancer treatment in the early 20th century considerable efforts have been made to maximize drug efficiency and at the same time minimize side effects. As there is a great interpatient variability in response to chemotherapy, the development of predictive biomarkers is an ambitious aim for the rapidly growing research area of personalized molecular medicine [9].

Methodology

The individual prediction of response will improve treatment and thus increase survival and life quality of patients. In the past, cell cultures were used as in vitro models to predict in vivo response to chemotherapy. Several in vitro chemo-sensitivity assays served as tools to measure miscellaneous endpoints such as DNA damage, apoptosis and cytotoxicity or growth inhibition [10]. Twenty years ago, the development of high-throughput technologies, e.g. cDNA microarrays enabled a more detailed analysis of drug responses. Thousands of genes were screened and expression levels were correlated to drug responses. In addition, mutation analysis became more and more important for the prediction of therapeutic success. Today, as research enters the area of -omics technologies, identification of signaling pathways is a tool to understand molecular mechanism underlying drug resistance. Combining new tissue models, e.g. 3D organoid cultures with modern technologies for biomarker discovery will offer new opportunities to identify new drug targets and in parallel predict individual responses to anticancer therapy. In this review, we present different currently used chemo-sensitivity assays including 2D and 3D cell culture models and several omics approaches for the discovery of predictive biomarkers. Furthermore, we discuss the potential of these assays and biomarkers to predict the clinical outcome of individual patients and future perspectives [11].

Discussion

Xenografts also have the ability to mimic the in vivo microenvironment of a tumour in a physiological context, regarding nutrient supply, angiogenesis etc. However, using this model, differences in metabolism, body size and genetic background between the host species and humans have to be considered. In summary, organoid cell cultures and xenografts represent valuable ‘‘bridge models’’ between in vitro cell lines and the clinical in vivo setting. The choice of a cell culture model for research should depend on the application in the study design and cost-benefit ratio. Over 60 years ago, the first human clonal cancer cell line was established from a patient’s tumors as shown in (Figure 1). Today, human tumour-derived clonal cell lines are able to grow in vitro, are easy to handle and thus they find wide application. Thousands of cell lines from diverse tumour entities can be purchased from different suppliers [12]. These cell lines are characterized and usually delivered including basic data, such as genetic profile, morphology, doubling time, cyto-genetics and references, by which additional data can be received using literature search. Being such robust and easy to handle models,

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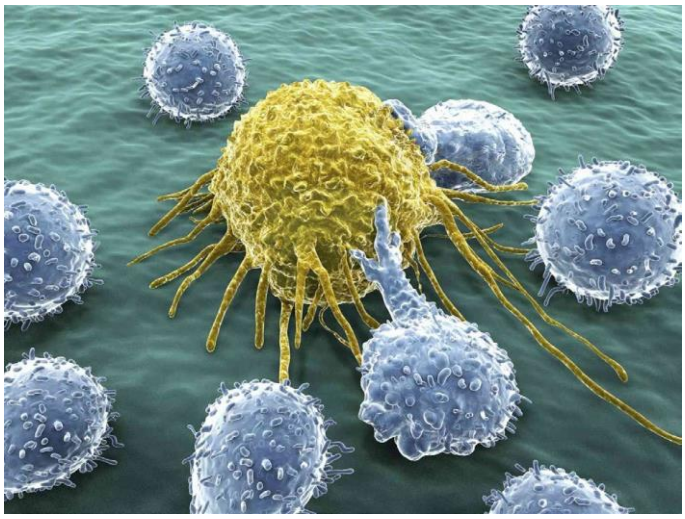

Figure 1: Malignant cells can invade tissues.

Figure 2: Malignant cells grow in an uncontrolled way.

secondary cell lines are a preferred starting point for the analysis of cellular mechanisms, e.g. resistance to anticancer therapy and signalling pathways. These models are also routinely used in versatile applications, e.g. testing of efficacy of compounds, examination of metastasis mechanisms, preparation of cellular compartments, extraction of proteins and DNA. Furthermore, secondary cell lines are well suited for artificial manipulation of cell characteristics, such as expression of mRNAs and proteins, mutations and modulation of chemo-sensitivity [13]. For example, approaches to understand acquired drug resistance are cancer cell lines with established drug resistance. Continuous exposure of these drug-sensitive cell lines to anticancer therapeutics in vitro, selects for the relatively rare drug-resistant clones, which are then further raised to a chemo-resistant sub clone cell line. Comparative analysis of properties of the parental drug-sensitive cell lines and the selected drug-resistant cell lines has the potential to identify specific molecular mechanisms of drug resistance. Hence, transformed cell lines and their parental counterparts are also commercially available and represent artificial, but defined models for the investigation of determinants of chemo-sensitivity. Nowadays, secondary cell lines are integrated in huge compound screening programs for drug discovery and research programs to understand the underlying mechanism of individual response to chemotherapy. Secondary cell lines fulfil all requirements for implementation in high-throughput screenings, enabling the rapid screening of large panels of compounds. The National Cancer Institute 60 platform was the first high-throughput cancer cell line screening program and therefore triggered the development of adequate techniques. The experimental methods had to be adapted to the requirements of economic, high-throughput screenings, e.g. high-content data mining, automation of handling liquids, miniaturization of cell culturing and drug testing procedures as shown in (Figure 2).

A major finding of the program was that compounds with similar patterns of cell line chemo-sensitivity tend to have common mechanism of action, which led to the development of new algorithms for data analysis and adaption of study designs [14]. The NCI60 anticancer drug discovery program was reviewed in detail by Shoemaker, who highlighted its history and methodology. Learning from the NCI60 experiences, the Cancer Chemotherapy Centre of the Japanese Foundation for Cancer Research established the JFCR-39 platform. This panel of 39 human tumour-derived cell lines included a subset of the NCI60 cell lines and additional gastric cancer cell lines. A new algorithm for data analysis enabled the comparison of newly screened compounds with previously screened compounds to discriminate between new or previously described modes of action. Using the compare algorithm and advanced data mining techniques, several new anticancer agents were identified. In drug discovery or predictive biomarker studies for the introduced targeted anticancer therapeutics, small panels of cancer cell lines cannot display the clinical activities of these compounds, which are often limited to small sub-groups of molecular-defined patients. Taking this into account, high-throughput screenings are now being adapted to much larger panels of cell lines. To capture the genetic heterogeneity among diverse cancers, Mc Dermott and colleagues developed an automated platform for the screening of the chemo-sensitivity of 500 solid cancer cell lines to kinase inhibitors. In this study, they observed the expected response rates with only small subgroups of cell lines showing responses to particular compounds. Therefore, a comprehensive cancer cell line platform was established, currently including 1,200 cancer cell lines. Due to the fact that only around 80 % of those secondary cancer cell lines are adaptable to high-throughput screening, mostly caused by technical limitations such as insufficient doubling times or atypical culture requirements, this panel is referred to as the Centre for molecular Therapeutics 1000. This cell line panel is currently being used to investigate the genetic determinants for chemo-sensitivity. First results from this large data sets showed that tumor-derived cell lines recapitulate clinical findings concerning responses to targeted inhibitors [15]. Another, very recent approach in generating primary cell lines for in vitro experiments has been introduced by Lui. This approach initially comprised a method to indefinitely extend the life span of primary human keratinocytes using both fibroblast feeder cells and a Rho-associated kinase inhibitor, and is also efficiently applicable to establish cell cultures from human and rodent tumors. This innovative technique provides significant opportunities for cellular diagnostics and molecular therapeutics, expands the value of bio-banking and has the potential to greatly improve personalized medicine. A general disadvantage of secondary cell lines is that they only represent one cell from a diverse tumour microenvironment which resembles the capabilities necessary for adapting to in vitro culture. It is still unclear in which manner adaption to in vitro culturing and multiple passaging influences cell characteristic/behaviour. The establishment and cultivation of primary mixed single cell cultures always have been quite complicated. Primary mixed cell cultures isolated from patient's tumors represent a wide spectrum of cell types abundant in vivo. This diverse mixture mainly consists of different epithelial- and mesenchymal cancer cells,

tumour associated stroma and immune cells. Therefore, these primary cell cultures more closely reflect the in vivo situation than secondary, clonal cell lines. However, several difficulties are still to overcome, while establishing primary mixed cultures. The basis for the preparation of primary, mixed cell cultures is vital tumour tissue and experience in cell culture handling. Besides the quality of tumour tissue, the method for preparation of single cells from a tumour, the surface preparation of cell culture dishes and finally the composition of the culture media are also essential parameters for a successful establishment of primary mixed cultures. The artificial shifts in and losses of cell populations, due to unnatural in vitro culturing and passaging, limits the maximal diversity of cell types to low passage primary, mixed cultures. Most studies using primary cells prepare cell cultures shortly after tumour resection and disseminate cells directly for experiments. Studies regarding the in vitro chemo-sensitivity of primary cells were conducted in different tumour entities e.g. small cell lung cancer, colorectal cancer, gastric cancer, Leukemia, ovarian cancer and head and neck cancer. One limiting factor is that, the diversity of cell types will decrease during in vitro cultivation, due to the dissimilar ability of different cell types to proliferate in vitro and survive passaging. Another issue limiting the predictive value of these cell cultures is the loss of the 3D architecture of the origin tumour. 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.

Conclusion

The awareness of the importance of the tumour microenvironment and the three-dimensional aspects of solid tumors, 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 tumors and implications on anticancer treatment

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Conflict of Interest

None

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