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Review Article

HUMAN CANCER CELLS LINE AND THEIR USES IN RESEARCH

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Abstract:

Human cancer cell lines are invaluable tools in cancer research, playing a pivotal role in signalling the complexities of tumor biology, investigating signalling pathways, drug discovery, and exploring immunotherapy approaches. Despite their limitations, they have significantly contributed to our understanding of cancer and have been instrumental in the development of new treatments. The emergence of advanced technologies, such as organoid cultures, organ-on-a-chip systems, and single-cell analysis, holds great promise for overcoming the limitations of traditional cell line models and providing more physiologically relevant platforms. These advancements have the potential to revolutionize cancer research, enhance our understanding of tumor heterogeneity, and pave the way for personalized medicine. With ongoing improvements in standardization and quality control, human cancer cell lines will continue to be indispensable in driving future advancements and improving patient outcomes in the battle against cancer.

Keywords: Cancer Cells, Tumor, Heterogeneity, Immunotherapy.

1. Introduction:

Human cancer cell lines are invaluable tools in cancer research, playing a crucial role in understanding the fundamental mechanisms of cancer development and progression. These cell lines are derived from cancerous tissues and possess unique characteristics that closely mimic the behaviour of cancer cells in the human body. By studying cancer cell lines, researchers can explore various aspects of cancer biology, such as tumor initiation, growth, metastasis, drug response, and resistance [1]. One of the significant advantages of using human cancer cell lines is their ability to provide a renewable and reproducible source of cancer cells for experimentation. Unlike primary tumor samples, which are limited in supply and difficult to maintain long-term, cell lines can

be cultured and propagated indefinitely. This feature allows researchers to conduct extensive studies over extended periods, facilitating the investigation of diverse aspects of cancer biology [1, 2]. Moreover, human cancer cell lines offer a standardized and controlled experimental system. These cells are often characterized extensively, including genomic profiling, histopathological analysis, and molecular profiling, which provides valuable information about their genetic alterations and molecular subtypes. Such comprehensive characterization allows researchers to select appropriate cell lines for specific research questions, ensuring reliable and relevant results.

Cancer cell lines also enable the evaluation of drug efficacy and toxicity, playing a crucial role in preclinical drug development. By exposing cancer cell lines to potential therapeutic agents, researchers can assess their effects on cell viability, proliferation, apoptosis, and other relevant endpoints. This information aids in identifying promising drug candidates and predicting their potential clinical success or failure. Additionally, cancer cell lines have contributed significantly to our understanding of cancer genetics and molecular biology. By studying these cells, researchers have identified numerous genetic mutations, aberrant signaling pathways, and molecular alterations that drive cancer development and progression. Insights gained from cancer cell lines have led to the discovery of novel therapeutic targets and the development of targeted therapies, revolutionizing cancer treatment approaches [3].

Furthermore, cancer cell lines serve as models for studying cancer heterogeneity, which refers to the diversity of cancer cells within a tumor. Tumors are comprised of heterogeneous cell populations with distinct characteristics and responses to therapies. By utilizing multiple cancer cell lines derived from different tumor types and stages, researchers can investigate the underlying mechanisms of intra-tumoral heterogeneity and its implications for treatment resistance and disease progression [4, 5].

2. ESTABLISHMENT AND MAINTENANCE OF CANCER CELL LINES:

Establishing and maintaining cancer cell lines require expertise, adherence to sterile techniques, and appropriate culture conditions to ensure the long-term viability and stability of the cells. These cell lines serve as valuable tools for cancer research, facilitating a better understanding of the disease and aiding in the development of novel therapeutic strategies. Establishment and maintenance of cancer cell lines involve a series of steps to obtain a sustainable and reproducible population of cancer cells for research purposes.

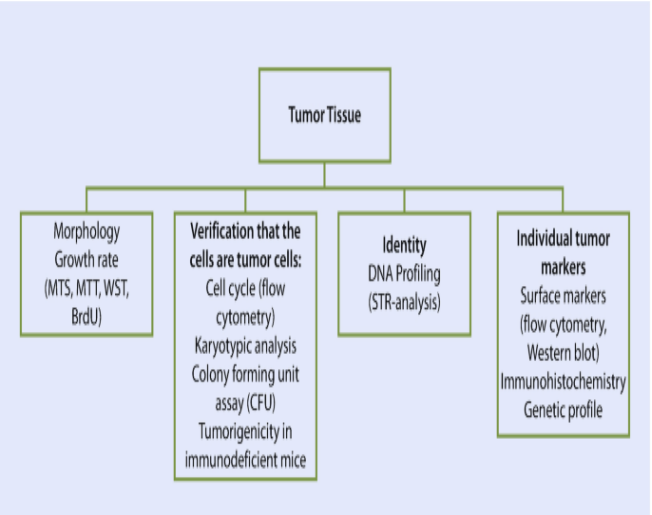

Fig.1: Establishment of tumor cell lines from primary tumor cell line [6]

Here is a general overview of the process:

2.1 Source of Cells:

Cancer cell lines can be derived from various sources, such as solid tumors or haematological malignancies. Tumor samples are obtained from surgical resections, biopsies, or sometimes from autopsy samples. These samples are collected following ethical guidelines and with appropriate informed consent [7].

2.2 Primary Culture:

Upon obtaining the tumor sample, it is processed in a sterile environment. The tissue is typically minced or disaggregated mechanically or enzymatically to obtain a single-cell suspension. The cells are then cultured in a suitable nutrient-rich medium containing growth factors, serum, and antibiotics. This initial culture is referred to as the primary culture [7, 8].

2.3 Immortalization:

Primary cultures have a limited lifespan and eventually undergo replicative senescence. To establish a cancer cell line, the cells need to be immortalized, allowing them to divide indefinitely. Immortalization can be achieved through various methods:

A. Spontaneous Immortalization: In some cases, cancer cells naturally acquire mutations that confer immortalization, such as activating mutations in telomerase or bypassing senescence checkpoints. These cells can be selected and expanded to establish a cell line.

B. Viral Transformation: Certain viruses, like Epstein-Barr virus (EBV) or human papillomavirus (HPV), can infect cancer cells and introduce genetic alterations that lead to immortalization. Viral transformation can be achieved by infecting the cells with the appropriate virus or introducing viral genes using recombinant techniques.

C. Induced Immortalization: Immortalization can also be induced artificially by introducing specific genes into the cells, such as the expression of telomerase or inactivation of tumor suppressor genes, using techniques like gene transfection or gene knockout [7, 8].

2.4 Culture Conditions:

Maintaining cancer cell lines requires optimal culture conditions. These conditions may vary depending on the specific cell line, but generally include:

A. Growth Medium: Cancer cells require a nutrient-rich growth medium supplemented with essential factors like growth factors, amino acids, vitamins, and minerals. Fetal bovine serum (FBS) or other serum substitutes are often added to provide necessary nutrients and growth-promoting factors.

B. Temperature and Atmospheric Conditions: Cancer cell lines are typically cultured at 37°C in a humidified incubator with a controlled atmosphere

containing 5% carbon dioxide (CO2). These conditions mimic the physiological environment necessary for their growth.

C. Sub culturing: Cancer cell lines need to be sub cultured regularly to prevent overcrowding and maintain their viability. This involves detaching the cells from the culture vessel using enzymatic or mechanical methods and transferring them to fresh culture vessels with a new growth medium.

D. Quality Control: Regular monitoring of cell line identity and characteristics is crucial. Authentication methods, such as DNA profiling or short tandem repeat (STR) analysis, can ensure the integrity and fidelity of the cell line over time [7].

3. CHARACTERIZATION OF CANCER CELL LINES [8, 9, 10]

Characterizing and authenticating cancer cell lines is crucial to ensure their identity, quality, and consistency for reliable research outcomes.

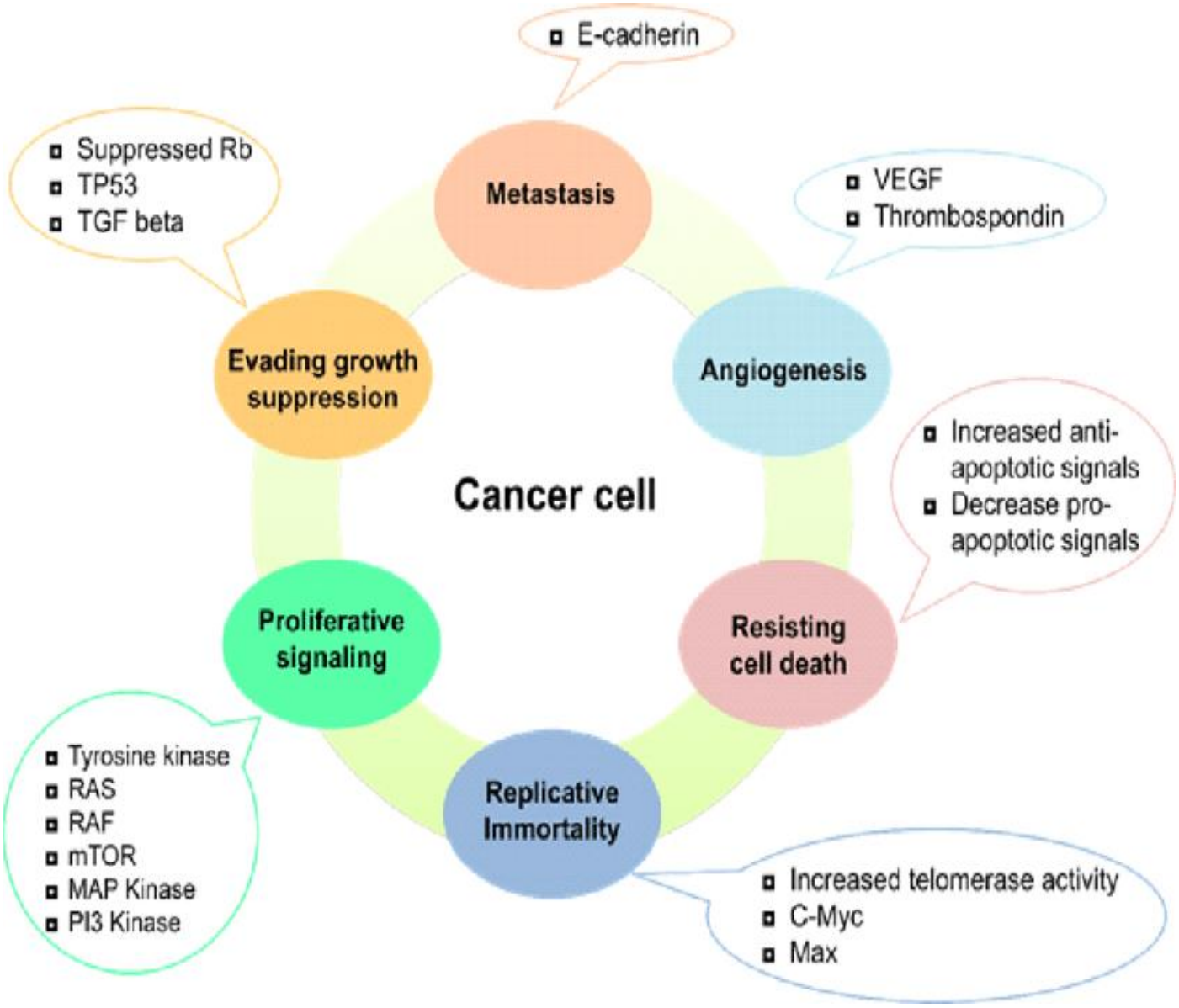

Fig.2: Characterization of cancer cell [11]

Several techniques are employed to assess the genetic and functional characteristics of cancer cell lines. Here are some commonly used methods:

3.1 DNA Profiling:

DNA profiling is a powerful technique used to authenticate cell lines by comparing the DNA profiles of the cell line with the original source material. It involves analysing specific genetic markers, such as short tandem repeat (STR) loci or single nucleotide polymorphisms (SNPs). The DNA profiles of the cell line are compared to known profiles of the donor tissue or previously authenticated cell lines to confirm their identity.

3.2 Genetic Analysis:

Genetic analysis methods provide insights into the genetic alterations present in cancer cell lines. These techniques include:

A. Karyotyping: Karyotyping involves examining the chromosomal composition and structure of cells. It helps identify chromosomal abnormalities, such as translocations, deletions, or duplications, which are common in cancer cells.

B. Fluorescence in situ Hybridization (FISH): FISH allows the visualization and detection of specific DNA sequences or genes within the cell. It is useful for identifying gene amplifications, deletions, or rearrangements associated with cancer.

C. Comparative Genomic Hybridization (CGH) or Array CGH: CGH techniques enable the detection of genomic imbalances, such as copy number alterations, across the entire genome. Array CGH provides higher resolution and can identify genetic alterations with greater precision.

D. Next-Generation Sequencing (NGS): NGS technologies can sequence the entire genome, exome, or transcriptome of cancer cell lines. This provides comprehensive information about genetic mutations, gene expression, and other genomic alterations.

3.3 Functional Assays:

Functional assays assess the behavior and characteristics of cancer cell lines. These assays evaluate various aspects, such as:

A. Proliferation and Viability Assays: These assays measure the rate of cell growth, viability, and response to different treatments or stimuli. Common assays include MTT assay, cell counting, or clonogenic assays.

B. Migration and Invasion Assays: These assays assess the ability of cancer cells to migrate and invade surrounding tissues. Trans well migration assays or Boyden chamber assays are commonly employed.

C. Drug Sensitivity and Resistance Assays: These assays determine the response of cancer cells to different therapeutic agents. They can help identify drug sensitivities, resistance mechanisms, and potential therapeutic targets.

D. Gene Expression Analysis: Techniques like quantitative real-time PCR (qRT-PCR) or RNA sequencing (RNA-seq) are used to analyze gene expression patterns, identifying differentially expressed genes or signaling pathways.

4. APPLICATIONS OF CANCER CELL LINES

By utilizing a combination of these techniques, researchers can comprehensively characterize and authenticate cancer cell lines, ensuring their validity and relevance for cancer research. These methods contribute to the reliability and reproducibility of experimental results and aid in the development of effective therapeutic strategies [11, 12, 13].

Cancer cell lines play a crucial role in elucidating signaling pathways involved in cancer development and progression. They serve as tools for studying the activation and regulation of oncogenic pathways, such as the MAPK/ERK, PI3K/AKT, Wnt/β-catenin, and Notch pathways. Manipulating these pathways in cancer cell lines can help unravel their roles in tumor growth, survival, and drug resistance, leading to the identification of potential therapeutic targets [14, 13, 15].

4.1 Drug Discovery and Development:

Cancer cell lines are essential in the early stages of drug discovery and development. They are utilized to screen and evaluate the efficacy of potential therapeutic agents against cancer cells. By exposing cancer cell lines to different compounds or drug candidates, researchers can assess their anti-proliferative effects, cytotoxicity, and ability to induce apoptosis. This enables the identification of promising compounds for further preclinical and clinical development [16].

4.2 Evaluation of Therapeutic Targets:

Human cancer cell lines are invaluable for investigating the validity and therapeutic potential of specific targets. By selectively targeting genes, proteins, or pathways in cancer cell lines, researchers can assess their impact on cellular processes and tumor growth. This information aids in validating potential therapeutic targets and guiding the development of targeted therapies [16].

4.3 Modelling Drug Responses and Resistance:

Cancer cell lines provide a platform for studying drug responses and resistance mechanisms. By exposing cancer cell lines to various therapeutic agents, researchers can determine their sensitivity or resistance profiles. These studies help identify predictive biomarkers of drug response and resistance, allowing for more personalized treatment strategies. Additionally, cancer cell lines can be manipulated to develop drug-resistant cell line models, enabling the investigation of resistance mechanisms and the development of strategies to overcome treatment resistance [17].

4.4 Immunotherapy Approaches:

Cancer cell lines are used to study and develop immunotherapy approaches for cancer treatment.

They serve as models for exploring immune checkpoint inhibitors, adoptive cell therapies, cancer vaccines, and other immunotherapeutic strategies. Cancer cell lines can be used to assess immune cell infiltration, evaluate immune response modifiers, and investigate the mechanisms of immunotherapy resistance [18, 19].

5. CONTRIBUTIONS TO PERSONALIZED MEDICINE

Cancer cell lines have made significant contributions to personalized medicine, particularly through the use of patient-derived xenograft (PDX) models and ex vivo drug sensitivity testing. These approaches offer valuable insights into individual patient responses to specific treatments and aid in tailoring therapies for improved patient outcomes [20]. Let's explore their contributions in more detail:

5.1 Patient-Derived Xenograft (PDX) Models: [21, 22, 23, 24]

PDX models involve implanting patient-derived tumor tissue directly into immunodeficient mice, allowing the tumor to grow and develop in an environment that closely mimics the human tumor microenvironment. PDX models retain the genetic and histopathological characteristics of the original patient tumor, making them valuable tools for personalized medicine. Their contributions include:

A. Predicting Drug Response: PDX models enable researchers to assess the response of an individual patient's tumor to different therapeutic agents or treatment combinations. By testing a range of drugs on PDX models, clinicians can obtain valuable information on drug efficacy, toxicity, and resistance specific to the patient's tumor.

B. Identifying Biomarkers: PDX models facilitate the identification of predictive biomarkers that correlate with treatment response or resistance. Analysis of gene expression, mutations, or protein expression patterns in PDX models can help identify biomarkers that guide treatment decisions and personalized therapy selection.

C. Preclinical Testing: PDX models serve as preclinical models for evaluating the efficacy and safety of novel therapeutic agents. They provide a bridge between in vitro studies and clinical trials, allowing researchers to gather crucial data on drug activity before advancing to human trials.

5.2 Ex Vivo Drug Sensitivity Testing: [25, 26]

Ex vivo drug sensitivity testing involves culturing patient-derived tumor cells or tumor fragments from biopsy or surgical samples and assessing their response to different drugs or treatment regimens. This approach offers the following contributions:

A. Personalized Treatment Selection: By testing a patient's tumor cells against a panel of drugs ex vivo, researchers can identify the most effective treatment options for that particular patient. This information helps guide personalized treatment

decisions, avoiding unnecessary exposure to ineffective therapies and optimizing treatment outcomes.

B. Rapid Screening: Ex vivo drug sensitivity testing allows for rapid screening of multiple drugs or drug combinations in a relatively short period. This accelerates the process of treatment decision-making, especially in cases where immediate therapy selection is critical.

C. Investigating Mechanisms of Resistance: Ex vivo drug sensitivity testing can help elucidate the mechanisms underlying treatment resistance in individual patients. By evaluating the response of tumor cells to different drugs, researchers can identify resistance patterns and explore potential strategies to overcome resistance. Both PDX models and ex vivo drug sensitivity testing contribute to personalized medicine by tailoring treatment strategies to the individual patient's tumor characteristics and responses. They provide valuable platforms for preclinical testing, treatment prediction, and understanding the underlying biology of tumors, ultimately improving patient outcomes in the era of personalized cancer care.

6. CHALLENGES AND LIMITATIONS [27, 28, 29, 30, 31]

Efforts are underway to address these limitations and improve the utility of cancer cell lines in research. Initiatives for better standardization, authentication, and quality control are being developed to ensure the reproducibility and reliability of cell line-based studies. Additionally, the integration of advanced technologies like single-cell sequencing and three-dimensional culture systems may help overcome some of the challenges associated with tumor heterogeneity and the in vitro environment.

Despite these limitations, cancer cell lines remain valuable models for hypothesis generation, mechanistic studies, and initial screening of therapeutic agents. However, their findings should be validated and further investigated using more representative models, such as patient-derived models or in vivo animal models, to ensure the clinical relevance of the research outcomes.

1. Representativeness of Tumours:

Cancer cell lines are derived from a single tumor sample, and therefore may not fully represent the complexity and heterogeneity of tumors in patients. Tumors are known to exhibit intratumoral and intratumoral heterogeneity, with diverse subpopulations of cells possessing distinct genetic and phenotypic characteristics. Cell lines may not fully capture this heterogeneity, potentially limiting their translational relevance.

2. Clonal Heterogeneity:

Cancer cell lines often undergo clonal selection during the establishment and maintenance process. This can result in the expansion of specific cell subpopulations and the loss of others, potentially altering the original tumor characteristics. The selected clones may not accurately represent the full spectrum of tumor cells and their responses to

treatments, limiting the generalizability of research findings.

3. Cross-Contamination and Misidentification:

Cross-contamination and misidentification of cell lines are significant concerns in cancer research. Contamination can occur during the handling, culture, or storage of cell lines, leading to the misidentification of cell lines or unintentional mixing of different cell lines. This can result in erroneous data interpretation and misleading research outcomes.

4. Lack of Standardization and Quality Control:

There is a need for improved standardization and quality control measures in cancer cell line research. Cell lines can exhibit genetic drift, phenotypic changes, or alterations in response to treatments over time. Additionally, there is a lack of uniform guidelines for authentication and quality control across research laboratories, leading to inconsistencies and potential inaccuracies in published data.

5. In vitro Environment:

Cancer cell lines are cultured in vitro, which is a simplified environment that does not fully recapitulate the complexities of the tumor microenvironment. The absence of stromal cells, immune cells, and extracellular matrix components can influence cell behaviour and drug responses, potentially limiting the translational value of in vitro findings.

6. Limited Clinical Correlation:

While cancer cell lines provide valuable insights into cancer biology and drug responses, their correlation with clinical outcomes in patients is not always straightforward. Factors such as differences in drug metabolism, host immune response, and tumor microenvironment interactions can contribute to disparities between in vitro findings and clinical efficacy.

7. EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS [32, 33, 34, 34, 36. 37]

Emerging technologies in human cancer cell line research offer exciting opportunities to overcome some of the limitations of traditional cell culture models and provide more physiologically relevant platforms for studying tumor biology and therapeutic responses. Here are three key emerging technologies and their potential impact:

1. Organoid Cultures:

Organoids are three-dimensional cell culture models that mimic the structural and functional characteristics of organs or tissues. In cancer research, tumor organoids derived from patient samples or cancer cell lines have gained popularity. These organoids recapitulate key features of tumors, including cellular heterogeneity, spatial organization, and complex interactions with the microenvironment. They offer a closer representation of the original tumor and can be used for drug screening, personalized medicine, and studying tumor-stroma interactions. Organoid

cultures hold promise for understanding tumor biology, testing novel therapies, and evaluating drug responses in a more clinically relevant context [34, 38].

2. Organ-on-a-Chip Systems:

Organ-on-a-chip systems are microfluidic devices that recreate the structure and function of human organs at a small scale. These systems consist of microchannel lined with living cells, allowing for the modelling of tissue-tissue interfaces, perfusion, and mechanical forces. In the context of cancer research, organ-on-a-chip platforms can replicate aspects of the tumor microenvironment, including blood vessels, immune cells, and extracellular matrix components. These systems enable the study of tumor invasion, angiogenesis, metastasis, and drug responses with improved physiological relevance. Organ-on-a-chip systems have the potential to enhance our understanding of tumor biology and accelerate drug development by providing more accurate and predictive models [39].

3. Single-Cell Analysis:

Single-cell analysis techniques have revolutionized our ability to study cellular heterogeneity and dynamics within tumors. By examining individual cells within a population, researchers can identify distinct subpopulations, uncover rare cell types, and characterize cellular states. Single-cell RNA sequencing (scRNA-seq) allows for the profiling of gene expression patterns at the single-cell level, providing insights into cell type identification, cellular transitions, and signaling pathways. Other single-cell analysis techniques, such as single-cell proteomics and single-cell epigenomics, offer additional layers of information. Single-cell analysis of cancer cell lines enables the identification of drug-resistant sub clones, the exploration of treatment-induced changes, and the discovery of novel therapeutic targets. This technology has the potential to advance personalized medicine by enabling the identification of unique molecular profiles and therapeutic vulnerabilities within individual tumors. These emerging technologies represent the future directions of human cancer cell line research, offering more sophisticated and representative models for studying tumor biology, therapeutic responses, and personalized medicine. Incorporating these technologies into cancer research workflows can enhance our understanding of cancer biology, improve drug discovery and development, and ultimately lead to more effective treatments for cancer patients [38,39].

Conclusion:

Human cancer cell lines have played a vital role in advancing cancer research by providing valuable models for studying tumor biology, investigating signaling pathways, drug discovery, evaluating therapeutic targets, modelling drug responses, and exploring immunotherapy approaches. Despite their limitations, cancer cell lines have significantly contributed to our understanding of cancer and the development of new treatments. Moreover, emerging technologies such as organoid

cultures, organ-on-a-chip systems, and single-cell analysis hold immense promise for overcoming the limitations of traditional cell line models and providing more physiologically relevant platforms. These advancements have the potential to further enhance our understanding of tumor heterogeneity, the tumor microenvironment, and personalized medicine. With ongoing efforts to improve standardization, authentication, and quality control, human cancer cell lines will continue to be indispensable tools in cancer research, driving future advancements and improving patient outcomes in the fight against cancer.

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