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Review Article

Exploring Breast Cancer Cells: Models, ER Resistance, and Research Benefits

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Abstract

Breast cancer is one of the biggest health issues in the world, and research on breast cancer cell models has helped us comprehend this complicated illness better. This work offers a thorough review of the many in vitro, in vivo, and three-dimensional culture models of breast cancer cells, emphasizing their special traits and research uses. The relevance of breast cancer cells in research is discussed in the introduction, which also highlights the value of various models in illuminating the underlying processes of the illness. The many breast cancer cell lines—MCF-7, T47D, MDA-MB-231, ZR-75-1, BT-474, and SK-BR-3, among others—are examined in Section 1; each has unique characteristics and a place in the field. The crucial problem of estrogen receptor (ER) resistance in the therapy of breast cancer is examined in Section 2. The processes behind ER resistance are discussed, along with how they affect treatment strategies and the course of the disease. The expression of ER in several breast cancer cell lines is further examined in Section 3, highlighting the distinctions between ER-positive and ER-negative subtypes and its implications for future study. In Section 4, the advantages of employing these breast cancer cell models are highlighted, with particular attention paid to how they promote personalized treatment, medication development and testing, and our understanding of disease pathways. The report also notes each model's shortcomings and difficulties, along with the ways in which researchers have dealt with them. The key breast cancer cell lines' creation tales are finally covered in full in Section 5, which also offers historical background and insights into the cell lines' relevance for breast cancer research. The importance of researching the variety of breast cancer cell models is emphasized in the paper's conclusion, which paves the path for future discoveries and encourages continued progress in our knowledge and management of this complicated illness.

Keywords: Breast Cancer; Cancer Cell Models; Estrogen Receptor (ER); ER Resistance; *In Vitro* Models; *In Vivo* Models; 3D Culture Models; Hormone Therapy; Signaling Pathways; Drug Resistance; Therapeutic Strategies

Introduction

Breast cancer is a serious illness that impacts a great number of people worldwide [1,7,8]. The medical profession has made significant efforts to comprehend and address this critical public health matter, despite the many obstacles it presents. Considerable progress has been achieved in establishing more effective medicines, increasing patient outcomes, and boosting diagnostic capacities via considerable research and clinical trials [1,9,10].

The cancer cells themselves and the models created to study them are at the center of this continuous fight against breast cancer [2,11,12]. These biological systems are vital research instruments that enable researchers to explore the complex relationship between genetic, cellular, and external variables that contribute to the onset and spread of breast cancer, as well as to assess novel therapeutic strategies [2,3,16].

Breast cancer cell models

Research on breast cancer is a complex and multifaceted field that uses several models to study different aspects of this crippling disease. Scientists often employ well described cell lines for breast cancer (e.g., MCF-7, T47D, MDA-MB-231, ZR-75-1, BT-474, and SK-BR-3) for in-depth study. These cell lines are widely used to study medicine sensitivity, pathways of signaling, and hormone sensitivity. They represent several molecular subtypes of breast cancer.

Animal models, particularly genetically modified mice, provide useful *in vivo* systems for examining the intricate process of tumor genesis and progression in addition to these *in vitro* models [3]. These animal models have made it possible for researchers to study the disorder more thoroughly and in a physiologically relevant setting [8].

In the field of breast cancer research, emerging 3D culture models like organoids and spheroids have also acquired significance [17-19]. These models allow researchers to study tumor-stroma connections, treatment response, and metastatic growth in a more realistic setting because they more properly depict the milieu around the tumor.

When considered together, these varied models are critical for better understanding the biology of breast cancer and evaluating potential therapeutic methods. The particular study issue and the component of breast cancer under investigation will determine which model is best since each method gives a different set of insights and viewpoints.

In Vitro models

MCF-7

The MCF-7 cell line originated from a 69-year-old Caucasian woman with metastatic breast cancer. It is an estrogen receptor (ER)-positive cell line, which means it expresses the estrogen receptor and is responsive to estrogen signaling. MCF-7 cells are widely used in breast cancer research as a model for studying hormone-responsive breast cancer, particularly in the context of endocrine therapy and estrogen-mediated signaling pathways [20,21].

T47D

The T47D cell line was derived from the pleural effusion of a 54-year-old woman with ductal carcinoma. Like MCF-7, T47D cells are also ER-positive, making them a useful model for studying hormone-responsive breast cancer. T47D cells are commonly used to investigate progesterone signaling and the effects of anti-progestin therapies [20].

MDA-MB-231

The MDA-MB-231 cell line was obtained from the pleural effusion of a 51-year-old woman with adenocarcinoma. In contrast to MCF-7 and T47D, MDA-MB-231 cells are ER-negative, representing a model of triple-negative breast cancer. This cell line is widely used to study late-stage, invasive breast cancer and to investigate the molecular mechanisms underlying metastasis [20].

ZR-75-1

The ZR-75-1 cell line was isolated from a 63-year-old Caucasian woman with ductal carcinoma. Like MCF-7 and T47D, ZR-75-1 cells are ER-positive and serve as a model for studying hormone-responsive breast cancer [22].

BT-474

The BT-474 cell line was derived from a 60-year-old woman with ductal carcinoma. BT-474 cells are ER-positive and also overexpress the HER2 (human epidermal growth factor receptor 2) protein, making them a model for HER2-positive breast cancer. This cell line is useful for investigating HER2-targeted therapies and the interplay between estrogen signaling and HER2 overexpression.

SK-BR-3

The 43-year-old Caucasian lady who had an adenocarcinoma was the source of the SK-BR-3 cell line. SK-BR-3 cells, which overexpress HER2 and are ER-negative in contrast to the preceding cell lines, constitute another model of HER2-positive breast cancer. Studies on the biology and therapeutic targeting of HER2-driven breast cancer frequently employ this cell line [22,23].

These several *in vitro* breast cancer cell lines, each with distinct properties, serve as useful models for examining various facets of the biology of breast cancer, including as hormone sensitivity, signaling pathways, and treatment vulnerabilities [22,23].

These diverse *in vitro* breast cancer cell lines, each with their unique characteristics, provide valuable models for investigating different aspects of breast cancer biology, including hormone responsiveness, signaling pathways, and therapeutic vulnerabilities.

In Vivo models

Researchers use animal models, especially genetically engineered mice, to study breast cancer in a more naturalistic, physiological setting in addition to researching the illness in lab settings utilizing cell cultures. These animal models enable researchers to examine the genesis, evolution, and metastasis of breast cancer tumors by simulating the intricate tumor microenvironment.

The MMTV-Neu transgenic mouse model is one instance; it overexpresses the HER2/Neu oncogene and forms tumors that resemble the HER2-positive subtype of breast cancer in humans. The MMTV-PyVMT transgenic mouse is an additional model that exhibits tumor development resembling the luminal subtype of breast cancer and expresses the middle T antigen of the polyoma virus [20,24].

These genetically modified mice models offer useful platforms for researching the molecular pathways behind breast cancer and assessing, in a whole-organism context, the efficacy of novel treatment strategies. By combining these *in vivo* models with *in vitro* cell line research, a holistic strategy for improving our knowledge and management of breast cancer is provided.

3D culture models

The introduction of three-dimensional (3D) culture models has transformed breast cancer research. Spheroids and organoids are the most common 3D culturing techniques.

Organoids are exceptional three-dimensional structures created by stem cells derived from embryonic or adult tissues. These self-organizing organoids can mimic the shape and function of the original breast tissue. Breast cancer organoids, for example, derived from patient tumor samples, may perfectly duplicate the original tumor's genetic features and variation. These models are critical for understanding the biology of breast cancer, assessing the efficacy of cancer treatments, and broadening the use of personalized medicine.

Conversely, spheroids are three-dimensional (3D) cancer cell groups that mimic the body's own natural tumor environment through self-assembly. Important aspects of tumor physiology, including as extracellular matrix signals, oxygen and nutrient gradients, and interactions between cancer cells, can be captured by breast cancer spheroids. For high-throughput drug screening and researching the origins of drug resistance, spheroids are essential.

These cutting-edge 3D culture models have helped researchers better understand the delicate nuances of breast cancer. This is intriguing because it might speed up the creation of more effective medications for patients.

Estrogen receptor (ER) resistance in breast cancer

Defining the Estrogen Receptor (ER) and its Role in Breast Cancer

Estrogen receptors (ERs) are like little locks found inside breast cancer cells. These locks can bind to the hormone estrogen, which acts like a key [5]. Normal breast cells and some breast cancer cells have these locks, and they need the estrogen keys to grow [5]. Breast cancer cells can have one lock, both locks, or no locks at all [5]. Cancers with the locks (ER-positive or ER+) can be treated with special drugs that either lower the amount of estrogen keys or block the locks from opening [5]. But breast cancers without the locks (ER-negative or ER) cannot be treated with these hormone therapies [5].

Differences between ER-positive and ER-negative breast cancer cells

Estrogen receptor (ER) positive carcinomas of the breast often develop more slowly than ER-negative cancers. Although the prognosis for women with ER-positive malignancies is typically better in the short term, these tumors can recur years after first therapy. Conversely, breast tumors that are ER-negative have a tendency to develop and spread more quickly. After therapy, these tumors frequently recur in the first few years. Younger women and members of particular racial and ethnic groups are also more likely to develop ER-negative malignancies [24]. The main distinction is that ER-positive tumors have a better short-term prognosis but may relapse later, whereas ER-negative cancers grow and spread more quickly, frequently returning within a few years following therapy. ER-negative malignancies are also more common in younger individuals and in specific demographic groups.

The Phenomenon of ER resistance in breast cancer treatment

For the treatment of ER-positive breast cancers, hormone therapy can be quite beneficial. Unfortunately, many patients eventually grow resistant to these medicines [24]. The problem of ER resistance is one that offers cause for alarm. It occurs when cancer cells manage to proliferate and disseminate despite the presence of anti-estrogen medications [24,26]. Since ER resistance lessens the efficacy of these crucial medicines, controlling hormone-sensitive

breast tumors is significantly hampered. Scholars are exerting great effort to get a deeper comprehension of the mechanisms underlying ER resistance, with the goal of creating novel approaches to surmount this challenge and enhance patient outcomes.

Mechanisms leading to ER resistance

A major reason for ER resistance in breast cancer is mutations in the ER-encoding gene (ESR1) [26]. These mutations can result in estrogen-independent growth and decreased susceptibility to anti-estrogen treatments, especially in the C-terminal helix 12 of the ER ligand-binding domain [26]. Additional elements that can lead to ER resistance include changes in ER expression levels and the initiation of different signaling pathways [24,26]. Developing more potent treatment plans for hormone-sensitive breast tumors requires a thorough understanding of the many processes behind ER resistance.

ER expression in breast cancer cells

ER expression in breast cancer subtypes

Breast cancer cells may be divided into several subtypes using three key proteins: human epidermal growth factor receptor 2 (HER2), oestrogen receptor (ER), and progesterone receptor (PR) [1]. The most common kind of breast cancer, ER-positive (ER+) breast cancer, makes up 70–80% of cases. These cancers are frequently less aggressive, express the estrogen receptor, and have a better prognosis [1,5]. However, 20–30% of cases of breast cancer are really ER-negative (ER-) tumors, meaning that they lack the estrogen receptor. These cancers are often more aggressive and have a worse prognosis [5]. For some severe forms of breast cancer, such triple-negative breast cancer, there are fewer particular therapy options. This is because they lack the HER2 expression [1,5].

Implications of ER expression on breast cancer behavior and treatment

The expression of oestrogen receptors in cancer cells has a substantial impact on breast cancer treatment and disease progression [1,5]. Aromatase inhibitors and selective estrogen receptor modulators (SERMs) are efficient at blocking or reducing estrogen signaling in ER-positive malignancies, hence halting tumor progression [5]. However, as the prior section revealed, certain ER-positive cancers may eventually develop resistance to these therapies [5]. However, because ER-negative breast cancers lack an estrogen receptor, endocrine medicines are ineffective in treating them. Instead, different treatments such as immunotherapy, chemotherapy, or targeted drugs are required [1,5].

Examples of ER-positive and ER-negative breast cancer cell lines

Well-characterized breast cancer cell lines are used by researchers to investigate the biology and possible therapeutic approaches for various disease subtypes [2]. A few ER-positive cell lines that are often used to study the processes behind ER-driven tumor growth and the emergence of endocrine therapy resistance are MCF-7, T-47D, and ZR-75-1. Nonetheless, MDA-MB-231, BT-549, and Hs 578T are ER-negative cell lines that are useful models for researching more aggressive subtypes of hormone-independent breast cancer and testing out new therapeutic approaches [2]. These cell line models aid in the development of more potent treatment strategies and a deeper comprehension of the biology of breast cancer when paired with further preclinical and clinical research.

Benefits of breast cancer cell models for scientists and researchers

Advantages of using different breast cancer cell models

Cell lines from breast cancer patients are very useful for scientists and researchers researching the condition [2]. There are several benefits associated with these well-characterized models, which comprise ER-positive and ER-negative subgroups. They offer a reliable and replenishable source of cells for research into the biology of breast cancer, the testing of novel treatments, and the study of drug resistance mechanisms [23]. Furthermore, the variety of breast cancer and the ways in which distinct subtypes react to different therapies may be studied by researchers thanks to the availability of numerous cell line panels.

Understanding disease mechanisms

Breast cancer cell lines play a crucial role in clarifying the intricate processes behind the onset and advancement of the illness [3]. These models may be used by researchers to investigate the biological processes, genetic changes, and signaling pathways that underlie the characteristics of cancer, including unchecked cell proliferation, invasion, and metastasis [3]. Through the comparison of ER-positive and ER-negative cell lines, researchers can acquire a deeper understanding of the unique biological traits and susceptibilities of various subtypes of breast cancer.

Drug testing and development

Breast cancer cell lines are essential for understanding drug resistance mechanisms and for preclinical testing of novel therapeutic agents [2,3]. With the use of these models, scientists may evaluate the effectiveness of new drugs, combinations, and targeted treatments—including those that particularly target the estrogen receptor pathway—by screening and testing them [27]. Additionally, researchers might find possible indicators and create plans to combat drug resistance by examining how different therapies affect ER-positive and ER-negative cell lines.

Personalized medicine

The advancement of customized medicine techniques is aided by the utilization of several breast cancer cell line models [28,29]. Through an awareness of the distinct traits and susceptibilities of various ER-positive and ER-negative subtypes, researchers can endeavor to customize therapeutic approaches according to the tumor profile of each patient specifically. This information can reduce the possibility of side effects, enhance treatment results, and assist pick the best medicines.

Challenges and limitations of breast cancer cell models

Although they are a useful research tool, breast cancer cell lines can have several drawbacks [28]. These models may not always correctly predict the *in vivo* response to therapies, nor may they adequately capture the complexity and variety of the tumor microenvironment. Furthermore, the cell lines may alter over time due to genetic drift and extended culture, which may have an impact on the cell lines' applicability and repeatability [30]. To overcome these obstacles, researchers frequently use supplementary strategies to confirm and corroborate the results of their cell line experiments, including organoids, clinical samples, and patient-derived xenograft models.

Origin stories of breast cancer cell lines

Major breast cancer cell line profiles

- **MCF-7:** The MCF-7 cell line, which was created in 1973 from a patient's pleural effusion who had metastatic breast cancer, is well-known for being estrogen receptor (ER) positive. It is a useful model for researching hormone response and developing endocrine therapy because of this feature [2].
- **T47D:** The T47D cell line, which was obtained from a pleural effusion in 1974, is ER-positive and a valuable resource for researching hormone treatments and their mechanisms of action [2].
- **MDA-MB-231:** The MDA-MB-231 cell line, which was isolated in 1973 and is triple-negative (ER, PR, and HER2 negative), is widely utilized in breast cancer research. This subtype is a useful model for researching new treatment strategies since it symbolizes more severe types of the illness and is frequently linked to a worse prognosis [2].
- **ZR-75-1:** The ER-positive ZR-75-1 cell line was created in the 1970s and has been widely used in hormonal research to further our knowledge of the biology of ER-driven breast cancer [2].
- **BT-474:** The BT-474 cell line, which originated from a metastatic location in 1978, is ER-positive and HER2-positive, which makes it a useful model for researching targeted medicines that target these two significant drivers of breast cancer [2].
- **SK-BR-3:** The SK-BR-3 cell line was isolated in 1970 and is useful for studying the biology of HER2-driven breast tumors as well as HER2-overexpressing and ER-negative therapies [2].

These important breast cancer cell lines' historical evolution and characterization have contributed significantly to our understanding of the illness. They have made it possible for researchers to examine the numerous subtypes of breast cancer, look into the underlying causes, and assess the effectiveness of different treatment modalities, all of which have advanced the field of breast cancer research and led to the creation of more potent medicines.

Conclusion

Summary of key points

This study has offered a thorough review of the significance of employing several breast cancer cell line models in research as well as the function of estrogen receptor (ER) expression in breast cancer. The concept and importance of the ER in breast cancer, the distinctions between ER-positive and ER-negative subtypes, and the occurrence of ER resistance in breast cancer therapy have all been covered. We have also looked at how ER expression affects the way breast cancer cells behave and respond to therapy, as well as the benefits and drawbacks of employing different breast cancer cell line models in research projects.

Importance of studying diverse breast cancer cell models

Our knowledge of the illness has advanced significantly because to the availability of a large variety of well-characterized breast cancer cell lines, including both ER-positive and ER-negative subtypes. These models have made it possible for scientists to investigate drug resistance methods, test novel treatments, and investigate the fundamental processes causing breast cancer. Through the use of these varied cell line panels, researchers may learn a great deal about the heterogeneity of breast cancer and create more individualized treatment plans depending on the features of each particular tumor.

Future directions and potential for new discoveries

The application of sophisticated cell line models in conjunction with other preclinical and clinical research will be essential in propelling future discoveries and advancements in patient care as breast cancer research develops. It is anticipated that further attempts to improve and broaden the range of breast cancer cell lines, together with the incorporation of multi-omics techniques and newer technologies, will provide fresh perspectives on the intricate biology of the illness. These developments will then open the door for the creation of more individualized and efficient treatment plans, which will eventually improve the prognosis for breast cancer patients.

Author Notes

Abdulghani A. Naeem and Saud A. Abdulsamad contributed equally to this work.

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