Elite Journal of Health Sciences. Volume 2 issue 1(2024), Pp. 20-24
https://epjournals.com/journals/EJHS

Genetic Heterogeneity in Breast Cancer: Implications

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Abstract

Breast cancer, a heterogeneous disease with diverse molecular subtypes, presents a complex challenge in the realm of oncology. The recognition of genetic heterogeneity within breast cancer has revolutionized our understanding of its etiology and progression. This review aims to elucidate the implications of genetic diversity in breast cancer for the development of effective treatment strategies. Advancements in genomic profiling have revealed distinct molecular subtypes, each characterized by unique genetic alterations and expression profiles. The heterogeneity observed in breast cancer extends beyond histological classifications, influencing clinical outcomes and responses to therapy. This review explores the underlying genetic drivers of breast cancer heterogeneity, including mutations in key oncogenes and tumor suppressor genes, as well as alterations in DNA repair pathways. This paper provides a comprehensive overview of genetic heterogeneity in breast cancer and its far-reaching implications for treatment strategies. By understanding the molecular intricacies driving this heterogeneity, clinicians and researchers can advance towards personalized and more effective therapeutic interventions, ultimately improving the prognosis and quality of life for individuals affected by breast cancer.

Keywords: *Breast cancer, Genetic heterogeneity, Molecular subtypes, Treatment strategies, Precision medicine, Targeted therapies, Clonal evolution*

Introduction

Breast cancer remains a formidable challenge in the realm of oncology, affecting millions of lives worldwide. The intricate nature of this disease is underscored by the diverse genetic landscapes it encompasses, giving rise to the phenomenon known as genetic heterogeneity. In recent years, the exploration of genetic heterogeneity in breast cancer has emerged as a pivotal avenue of research, holding profound implications for the development and refinement of treatment strategies.[1-5] The understanding of breast cancer has evolved beyond a singular, homogenous entity to a mosaic of distinct molecular subtypes. Genetic heterogeneity refers to the presence of varied genetic alterations and expressions within breast cancer tumors across different individuals. This diversity poses a challenge in devising effective and targeted treatment approaches, as the one-size-fits-all paradigm proves increasingly inadequate. Thus, unraveling the intricacies of genetic heterogeneity becomes imperative in tailoring interventions to the unique genetic profiles of individual patients.[6]

Breast cancer is typically a highly heterogeneous disease. Breast tumor heterogeneity has been observed and described since the nineteenth century and these differences have served as the basis for disease classification in 1988 reported variations in estrogen receptor concentration due to variations in tissue cellularity. Breast tumor heterogeneity was observed among different patients (inter-tumor heterogeneity) and even within each individual tumor (intra-tumor heterogeneity),

occurring as spatial and temporal heterogeneity. The spatial heterogeneity involves distinct areas within a tumor that have differences at the phenotypic, transcriptomic, epigenetic and genomic levels; the temporal heterogeneity refers to variations occurring over time during tumor progression between primary and metastasis or among different metastatic lesions.

Breast Cancer: Epidemiology and Risk Factors

Breast cancer is the most commonly diagnosed cancer of all cancers in women. It comprises 25% both in the developed and less developed world. It comes next to lung cancer as an overall cause of death for women (15.4% in more developed and 14.3% in less developed world).[7] Around the world, there is no population and woman with a truly low risk of developing breast cancer these days. Since the 2008 estimates by GLOBOCAN (an International Agency for Research on Cancer—IARC), both breast cancer incidence and mortality have increased by more than 20% and 14%, respectively. The incidence rate of breast cancer varies from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. Better awareness about the disease, identification of its early signs, and availability of screening programs are contributing to variable incidence rates across different regions of the world. In most of the developing regions, the incidence rates are below 40 per 100,000. In advanced breast cancer, brain metastases develop in approximately 10–16% of patients and are associated with poor prognosis and survival. Different subtypes of breast cancer are associated with different risks of developing central nervous system metastases.[8]

Mortality is relatively low in most of the low-incidence countries, but the likelihood that an individual dies of breast cancer is much higher (nearly 17%) in low-incidence countries than in high-incidence countries.[9] The reasons for the differential survival are multiple and include cultural influences, stage of presentation, and standards of healthcare. Among the established risk factors are being a female, early onset of menstruation, late onset of menopause, long menstrual history, use of oral contraceptives, never having children/having them later in life, age, family history, genetics, personal history of breast cancer, radiation to chest or face before age of 30, race/ethnicity, pregnancy, and breastfeeding. Potentially avoidable risk factors include overweight/obesity, using hormone replacement therapy (HRT), drinking alcohol, smoking, and lack of exercise. Low levels of vitamin D light exposure at night, certain kinds of noncancerous breast diseases, and exposure to multiple sources of polycyclic aromatic hydrocarbons from the environment are among the emerging risk factors for breast cancer.

Male breast cancer is an uncommon form that comprises less than 1% of all breast cancers globally, although an increasing trend in incidence is seen recently. Due to its rarity, there are few clinical trials, and many clinical recommendations are, hence, derived from studies of female breast cancer. Relatively little is known about the etiology of male breast cancer. Epidemiologic risk factors for male breast cancer encompass disorders related with hormonal imbalances and radiation exposure.[10]

Diversity in Tumors of Breast Cancer and the Mechanisms of Heterogeneity

Human breast cancer is a group of highly heterogeneous lesions of about 20 different subtypes, morphologically.[11] It is highly heterogeneous in terms of its etiology and pathological characteristics, and some show slow growth with excellent prognosis, whereas others are clinically aggressive. Understanding the specific driving forces behind different subtypes of cancer is indispensable for better management of the disease. Besides, development of more effective

treatments against breast cancer necessitates thorough understanding of the molecular mechanisms involved in breast tumor development and the acquisition of malignancy.

The mechanisms accounting for breast cancer heterogeneity remain elusive.[12] However, two conventional theories (clonal evolution and CSC) hold possible explanations. The clonal evolution theory is the first model to describe a way in which cancer cells with diverse phenotypes could arise within a tumor. It states that distinct cancer cell populations evolve progressively due to heritable genetic and epigenetic changes during a multistep tumorigenesis process. These random events create conducive environment for the selection and clonal outgrowth of novel cell populations resulting from accumulating mutations.

The CSC model suggests that cancer cells with similar genetic backgrounds can be hierarchically organized according to their tumorigenic potential.1[3] Accordingly, CSCs reside at the apex of the hierarchy and are thought to possess the majority of a cancer's tumor-initiating and metastatic ability. Unidirectional nature is a defining feature of the CSC model, whereby they undergo symmetric division to replenish the CSC pool and irreversible asymmetric division to generate daughter cells (non-CSCs) with low tumorigenic potential. Tumorigenic cells can be distinguished from nontumorigenic cells based on marker expression by the CSCs. Both proponents argue that the tumor microenvironment substantially influences the processes of carcinogenesis and tumor progression.

The plastic CSC theory, a third and evolving model, states that bidirectional conversions exist between non-CSCs and CSCs. According to this model, the missing link between the two conventional models is that non-stem cells and non-CSCs can undergo a dedifferentiation process and reenter the stem cell/CSC state due to aberrant changes in gene expression. Factors such as hepatocyte growth factor (HGF), CXC chemokine receptor-7 (CXCR7), and IL-6, which are derived from mesenchymal cells, contribute for the dedifferentiation. Microenvironment specific for the individual tumor affects the plasticity-driven CSC niche, and an understanding of this phenomenon is critical for developing a more effective cancer treatment.[13]

Implications of Intratumorally Heterogeneity for Cancer Treatment

Intertumoral heterogeneity arises due to complex genetic, epigenetic, and protein modifications resulting in phenotypic selection in response to environmental insult. This feature gives the tumor significant adaptability to thrive under unfamiliar conditions such as hypoxia or chemical weaponry.[14] Cell-to-cell variability, either genetic or not, can compromise responses to cancer therapies by increasing the repertoire of possible cellular responses. One of the clinical implications of intertumoral heterogeneity is drug resistance and treatment failure. Therefore, identification of intertumoral heterogeneity, which represents genetic characteristics of different cell subpopulations within the primary tumor, could provide important clinical implications to overcome this considerable challenge. CSCs and interaction with their nurturing microenvironment (niche) were implicated as potential mechanisms underlying the intratumoral heterogeneity, and destroying these tumor microenvironments is recently considered to be one of the therapeutic targets against CSCs. The hypothetical implication of this heterogeneity on therapeutic approach may include either concurrent combination or sequential treatments with multiple mutation-targeting agents.[13] Targeting these breast CSCs with therapeutics could be instrumental to achieve durable clinical responses. Therefore, expanded understanding of biology of breast CSCs and their key signaling pathways, molecular diagnosis of breast tumors, and

identification of appropriate clinical trial endpoints are essential for the development of CSC targeting agents.

Biology and Biomarkers of Breast CSCs

Stem cells are undifferentiated cells defined by their properties of self-renewal and potency and are rare in nature.[15] Breast cancers contain CSCs, and these cells are thought to be involved in tumor initiation, progression, evolution, and metastasis. CSCs were first identified in acute myeloid leukemia in 1994 and are defined by their unlimited self-renewal ability and their capacity to initiate and maintain malignancy. CSCs, typically constituting 1–5 % (could be as high as 11–35 % in breast cancer) of the tumor size, are tumorigenic multipotential cells with dysregulated self-renewal properties in which upon division, one daughter cell retains stemness and the other becomes committed to a lineage. Characteristically, these cells are slow-dividing and have a lower ability to undergo apoptosis and a higher ability of DNA repair. Breast CSCs are the best characterized subpopulations being the first CSCs prospectively demonstrated in human solid tumors. Correlation between epithelial-to-mesenchymal transition (EMT) and CSCs was reported, and CSCs displaying mesenchymal characteristics are resistant to chemo- and radiotherapy and are considered responsible for recurrence of the disease after treatment. The EMT promotes cancer cell migration and invasion resulting in the reconstitution of metastatic colonies at distant sites.[15]

CSC Signaling Pathways as a Potential Target for Cancer Treatment

Conventional therapies against cancer have multiple limitations that lead to treatment failure and cancer recurrence. Dysregulation of signal pathway network plays an important role in retaining the stemness of CSCs and thus can possibly be eradicated by targeted therapeutics against those signaling pathways. The signaling pathways which are crucial for the biological functions of normal stem cells are abnormally activated or repressed in CSCs. Distinct and specific surface biomarker phenotypes and upregulated intracellular features can be used to distinguish CSCs from normal stem cells. Seemingly, in addition, CSCs have their own specific enhanced signaling pathways. They are also protected against xenobiotics by the high expression of ATP-binding cassette (ABC) transporter proteins, the characteristic feature that differentiates the CSCs from normal cells. Targeting these transporter proteins can be one of the key strategies to overcome resistance to chemotherapy.[13]

Conclusion

The recognition of genetic heterogeneity in breast cancer has transformed our understanding of this complex disease and has profound implications for treatment strategies. The delineation of distinct molecular subtypes and the identification of specific genetic alterations have paved the way for a more personalized and targeted approach to breast cancer therapy. Precision medicine, with its focus on tailoring treatments to the individual genetic makeup of tumors, holds great promise in improving treatment efficacy while minimizing adverse effects.

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