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Genetic Influence on Breast Cancer Progression: A Molecular Perspective

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Abstract

Breast cancer is a complex and heterogeneous disease with various clinical outcomes, and its progression is influenced by a multitude of factors, including genetic components. This paper explores the molecular perspective of genetic influences on breast cancer progression, aiming to enhance our understanding of the underlying mechanisms driving the disease. The intricate interplay between inherited genetic mutations and sporadic genetic alterations within breast cancer cells significantly contributes to the initiation, development, and metastasis of the disease. We delve into the role of key genes involved in the regulation of cell cycle, DNA repair, and tumor suppression, shedding light on their impact on breast cancer pathogenesis. In conclusion, this review consolidates current knowledge on the genetic determinants of breast cancer progression from a molecular standpoint. The insights gained from unraveling the genetic intricacies of breast cancer pave the way for innovative diagnostic and therapeutic approaches, ultimately contributing to improved patient outcomes and a more comprehensive understanding of this formidable disease.

Keywords*: genetics, breast cancer, molecular perspective*

Introduction

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most common cause of death from cancer among women in the world. Anatomically, the breast has milk-producing glands in front of the chest wall. They lie on the pectoralis major muscle, and there are ligaments support the breast and attach it to the chest wall. Fifteen to 20 lobes circularly arranged to form the breast. The fat that covers the lobes determines the breast size and shape. Each lobe is formed by lobules containing the glands responsible for milk production in response to hormone stimulation. Breast cancer always evolves silently. Most of the patients discover their disease during their routine screening. Others may present with an accidentally discovered breast lump, change of breast shape or size, or nipple discharge. However, mastalgia is not uncommon. Physical examination, imaging, especially mammography, and tissue biopsy must be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumor tends to spread lymphatically and hematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs.[1-4]

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Female breast cancer risk is affected by the reproductive history. The hormonal background also influences the course of the disease. The female reproductive hormones such as estrogens, progesterone, and prolactin have a major impact on breast cancer and control postnatal mammary gland development.[5] Most of the hormonal risk factors are associated with estrogen hormone. Prolonged exposure to estrogen is known to be associated with elevated levels of breast cancer risk. Factors such as early age at menarche, late onset of menopause, long menstrual history, nulliparity, recent use of postmenopausal hormone therapy or oral contraceptives, late age at first birth, and obesity are considered as hormonal risk factors.[6] There are a number of nonhormonal risk factors associated with the development of breast cancer, which are indirectly attached to modulate the estrogen exposure, such as age at exposure to ionizing radiation, alcohol consumption, and dietary factors.

The involvement of genetic factors in racial and ethnic differences in health and disease is currently the focus of intense scrutiny. There are numerous dimensions to this issue. Some have questioned the utility or meaningfulness of the race concept in addressing health and required that submitted manuscripts explain and justify the study of particular ethnic groups or populations. At the same time, other researchers report that conventionally defined racial groups differ in genetic factors that affect risk for specific diseases or sensitivity to therapeutic drugs. Still others have presented the case that racial categories may have biological meaning and can be valuable in biomedical research.[7]

The term race is used in a great variety of ways. Common usage may differ from that of policy makers, and scholarly usage may also vary considerably. Genetic conceptualizations of race, in particular, make reference to differences between and among populations in gene frequencies. The subdiscipline of population genetics is explicitly concerned with such differences and with the dynamics of processes, such as mutation, differential survival, the reproduction of particular gene variants, gene flows between populations through migration, and similar matters.[8]

Tumor initiation and progression

For many years, breast cancer has had the highest incidence of all cancers in women worldwide.[9] Patients have better survival compared with more fatal cancers possibly because the breast tissue is physically not a necessary organ for human survival. Yet the mental and emotional disturbances from major surgeries as well as deaths by relapse or metastasis seriously endanger women's health. Since the earliest known descriptions of breast cancer originating in ancient Egypt, people have been dedicated to finding means of eradicating this disease. Leaps and bounds have been made in terms of this endeavor, especially in recent years. Mastectomy and chemotherapy have greatly improved the survival of breast cancer patients and more elegant forms of surgical procedures are now being applied to minimize the post-treatment psychological impact. However, without fully understanding the underlying mechanism and pathogenesis, the efficiency of prevention and treatment will always be limited.

Breast cancer is a compilation of distinct malignancies that manifests in the mammary glands. Carcinomas make up the majority of breast cancers while sarcomas such as phyllodes tumors and angiosarcomas are rarely seen.[10] Thanks to the rapid progresses in molecular biology, systems biology and genome sciences in the past decades, our understanding about this disease has been dramatically expanded at cellular, molecular and genomic levels. Here, we intend to provide a comprehensive up-to-date overview of the basic biological aspects of breast cancer, including the

risk factors, specific breast cancer classifications and subtypes, possible roles of mammary stem cells in breast cancer, major signaling pathways in breast cancer development, common gene mutations in breast cancer, the regulatory roles of epigenetics and noncoding RNAs in breast cancer, the molecular basis of triple-negative breast cancer, tumor heterogeneity of breast cancer, and the mechanism underlying breast cancer metastasis. It is our goal to present the aforementioned information in hopes of disseminating the present understanding of the molecular and genetic bases of breast cancer, which can be employed to assist in the development of novel and targeted therapies as a means of realizing the full potential of personalized medicine for breast cancer.

Key Genetic players

BRCA1 and *BRCA2* are tumor suppressor genes, familial mutations in which account for ∼5% of breast cancer cases in the USA annually.[11] Germ line mutations in *BRCA1* that truncate or inactivate the protein led to a cumulative risk of breast cancer, by age 70, of up to 80%, whereas the risk of ovarian cancer is 30–40%. For germ line *BRCA2* mutations, the breast cancer cumulative risk approaches 50%, whereas for ovarian cancers, it is between 10 and 15%. Like *BRCA1* mutations, which almost exclusively result in female breast and ovarian cancers, *BRCA2* families also show a marked increase in breast and ovarian cancer. However, unlike *BRCA1* families, they exhibit an increased risk of male breast, pancreas and prostate cancers. Tumors of patients from *BRCA1* and *2* families typically exhibit a loss of heterozygosity or other somatic alterations of *BRCA1* and *2* respectively, with the wild-type copy being lost. Both BRCA1 and BRCA2 are involved in maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps. Not surprisingly, the complete loss of function of either protein leads to a dramatic increase in genomic instability. How they function in maintaining genome integrity after the onset of DNA damage will be the focus of this revie.

Genetic Biomarkers

Genomic biomarkers for breast cancer are comprised of rare highly penetrant mutations of genes such as *BRCA1* or *BRCA2*, moderately penetrant mutations of genes such as *CHEK2*, as well as more common genomic variants, including single nucleotide polymorphisms, associated with modest effect sizes.[12] When applied in the context of appropriate counseling and interpretation, identification of genomic biomarkers of inherited risk for breast cancer may decrease morbidity and mortality, allow for definitive prevention through assisted reproduction, and serve as a guide to targeted therapy.

Conclusion

The molecular perspective on genetic influences in breast cancer progression underscores the complexity of the disease and highlights the critical role played by genetic factors in shaping its course. The exploration of key genes involved in various cellular processes provides a nuanced understanding of the mechanisms underpinning tumor initiation, growth, and metastasis. The integration of genetic profiling and personalized medicine strategies represents a paradigm shift in breast cancer research and clinical management. Identifying specific genetic signatures associated with aggressive tumor behavior enables more precise diagnostics and tailored treatment

approaches. This not only enhances the efficacy of interventions but also minimizes potential side effects, offering a more patient-centric approach to breast cancer care.

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