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Estrogen and BRCA1 Deficiency Work Together to Cause Breast Cancer Mutation-Related DNA Damage

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Abstract

Breast cancer, a complex and heterogeneous disease, is influenced by various genetic, hormonal, and environmental factors. Among these, the interplay between estrogen signaling and the tumor suppressor gene BRCA1 has garnered significant attention due to their individual roles in breast cancer etiology. Estrogen, a pivotal hormone in mammary gland development and function, has been associated with increased breast cancer risk, primarily through its mitogenic and pro-survival effects. On the other hand, BRCA1 plays a critical role in maintaining genomic stability and facilitating DNA repair processes. Mutations in BRCA1 are strongly linked to hereditary breast and ovarian cancers. Recent research suggests a multifaceted interaction between estrogen signaling and BRCA1 function, particularly in the context of DNA damage and repair mechanisms. This review delves into the intricate relationship between estrogen and BRCA1 deficiency, emphasizing their collaborative role in driving breast cancer-associated DNA damage and mutagenesis. We explore the molecular mechanisms through which estrogen can compromise BRCA1-mediated DNA repair, potentially leading to the accumulation of deleterious mutations. Furthermore, we discuss the implications of this synergistic interplay for therapeutic strategies targeting hormone receptor-positive breast cancers with BRCA1 mutations. Enhancing our understanding of how estrogen and BRCA1 deficiency coalesce to promote mutation-related DNA damage is crucial for developing more effective preventive and treatment approaches for breast cancer.

Keywords: Estrogen; BRCA1 deficiency; Breast cancer; DNA damage; DNA repair; Hormonal signaling

Introduction

Breast cancer remains a foremost global health concern, accounting for a substantial proportion of cancer-related morbidity and mortality among women. The etiology of breast cancer is multifaceted, encompassing genetic predisposition, hormonal imbalances, and environmental influences [1]. Among the multitude of factors contributing to its pathogenesis, the intricate interplay between estrogen signaling and the tumor suppressor gene BRCA1 has garnered considerable attention. Estrogen, a pivotal hormone in mammary gland development and homeostasis, exerts diverse effects on cellular proliferation, differentiation, and survival. Its significance in breast cancer is underscored by the observation that hormone receptor-positive (HR-positive) breast cancers, characterized by estrogen receptor (ER) expression, constitute the most prevalent subtype. Concurrently, BRCA1 has emerged as a central guardian of genomic stability, orchestrating key mechanisms that repair DNA damage and prevent the accumulation of mutations [2]. Loss-of-function mutations in the BRCA1 gene confer a significantly elevated risk of hereditary breast and ovarian cancers, highlighting its critical role in tumor suppression. Recent research has unveiled intricate crosstalk between estrogen signaling and BRCA1 function, particularly in the context of DNA damage and repair mechanisms. While estrogen promotes cellular proliferation and survival, BRCA1 counters these effects by orchestrating DNA repair processes, thereby maintaining genomic integrity [3]. This review aims to elucidate the synergistic relationship between estrogen and BRCA1 deficiency in the context of breast cancer-associated DNA damage and mutation. We delve into the molecular mechanisms through which estrogen may compromise BRCA1-mediated DNA repair, potentially fostering the accumulation of deleterious genetic alterations. By dissecting this complex interplay, we aim to provide a comprehensive understanding of how estrogen and BRCA1 deficiency collaborate to drive mutation-related DNA damage in breast cancer. Such insights hold paramount importance for refining therapeutic strategies, especially in HR-positive breast cancers harboring BRCA1 mutations [4]. As we uncover the intricate dynamics of these pathways, we pave the way for more effective preventive and treatment modalities targeting this formidable disease.

Discussion

The intricate interplay between estrogen signaling and BRCA1 function presents a compelling avenue for understanding the mechanisms underlying breast cancer mutation-related DNA damage. The convergence of these two influential factors adds a layer of complexity to the already intricate landscape of breast cancer pathogenesis [5]. In this discussion, we delve into the multifaceted ways in which estrogen and BRCA1 deficiency collaboratively contribute to DNA damage accumulation, with implications for therapeutic strategies.

Estrogen-mediated DNA damage: Estrogen's role in promoting cell proliferation and survival is well-documented, with the hormone driving cell cycle progression and inhibiting apoptosis. However, emerging evidence suggests that estrogen exposure might also contribute to DNA damage [6]. Estrogen-induced oxidative stress and genotoxic effects could lead to DNA lesions, straining the DNA repair machinery. In cases where BRCA1 function is compromised, the timely and accurate repair of these lesions could be hindered, allowing for the accumulation of mutations.

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BRCA1 dysfunction and DNA repair impairment: BRCA1 plays a pivotal role in homologous recombination (HR)-mediated DNA repair, a high-fidelity mechanism for repairing double-strand breaks. Deficiency in BRCA1 function leads to defective HR, forcing cells to rely on error-prone alternative repair pathways, such as non-homologous end joining [7]. This shift increases the likelihood of mutations, contributing to genomic instability. The simultaneous presence of estrogen, particularly in ER-positive breast cancers, further challenges the already compromised DNA repair capacity of BRCA1-deficient cells.

Crosstalk and synergism: Beyond their individual roles, estrogen and BRCA1 appear to engage in crosstalk that influences DNA damage and repair pathways. Estrogen signaling has been demonstrated to modulate BRCA1 expression levels, potentially impacting the availability of this critical DNA repair factor [8]. Moreover, estrogen receptor alpha (ERα) has been found to directly interact with BRCA1, suggesting a possible regulatory relationship that influences the DNA damage response.

Therapeutic implications: The identification of this synergistic interplay between estrogen and BRCA1 deficiency has important therapeutic implications, particularly for HR-positive breast cancers harbouring BRCA1 mutations [9]. Targeted therapies that exploit the vulnerabilities arising from this interaction could offer new avenues for treatment. Strategies that inhibit estrogen signaling, combined with agents that selectively target DNA repair pathways, could potentially sensitize tumor cells to therapy while sparing normal tissue.

Personalized approaches: As we unveil the complexities of estrogen-BRCA1 interplay, the notion of personalized medicine gains prominence. Patient stratification based on the status of estrogen signaling, BRCA1 function, and DNA repair proficiency could guide treatment decisions [10]. Identifying patients who might benefit from a combined approach of endocrine therapy and DNA repair-targeted agents holds promise for improving treatment outcomes.

Conclusion

In conclusion, the convergence of estrogen signaling and BRCA1 deficiency offers a compelling perspective on the molecular underpinnings of breast cancer mutation-related DNA damage. The intricate interplay between these factors contributes to the initiation and progression of breast cancer, and the therapeutic strategies derived from this understanding hold significant promise in improving patient outcomes. As research in this field progresses, we are poised to uncover novel insights that could revolutionize our approach to managing breast cancer and potentially extend these findings to other hormone-driven cancers. The intricate balance between estrogen's pro-survival and mitogenic effects and BRCA1's role in maintaining genomic stability creates a delicate equilibrium that, when disrupted, can lead to mutation-related DNA damage and oncogenic transformation. The collaborative action of these factors underscores the complexity of breast cancer etiology, especially in hormone receptor-positive breast cancers with BRCA1 mutations. The therapeutic implications of understanding this interplay are profound. Targeted therapies that exploit the vulnerabilities arising from estrogen-BRCA1 synergism hold promise, offering a more personalized and effective approach to treatment. The collaborative efforts of researchers, clinicians, and policymakers to translate this knowledge into innovative therapeutic strategies have the potential to revolutionize breast cancer management, improving patient outcomes and advancing our broader understanding of hormone-driven cancers.

Conflict of Interest

None

Acknowledgment

None

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