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BRCA mutations, homologous recombination deficiency, and PARP inhibitor resistance in ovarian cancer

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Abstract

Ovarian cancer remains one of the most lethal gynecologic malignancies worldwide, largely due to late-stage diagnosis and the eventual development of therapeutic resistance. A major breakthrough in its management has been the identification of defects in homologous recombination repair, particularly those involving BRCA1 and BRCA2 mutations. These discoveries have led to the clinical adoption of poly (ADP-ribose) polymerase (PARP) inhibitors, which exploit synthetic lethality in tumors harboring homologous recombination deficiency. Despite significant improvements in progression-free survival, resistance to PARP inhibitors has emerged as a major clinical challenge. This review explores the molecular basis of BRCA mutations and homologous recombination deficiency in ovarian cancer, the mechanisms of action of PARP inhibitors, and the evolving landscape of resistance mechanisms. It also discusses emerging therapeutic strategies aimed at overcoming resistance and improving patient outcomes.

Keywords: Ovarian Cancer; BRCA1; BRCA2; Homologous Recombination Deficiency; PARP Inhibitors; Resistance Mechanisms; DNA Repair; Synthetic Lethality

1. Introduction

Ovarian cancer is a heterogeneous disease with high-grade serous ovarian carcinoma representing the most common and aggressive subtype [1, 2]. The majority of patients present with advanced-stage disease, contributing to poor survival rates [3]. Over the past two decades, advances in molecular oncology have reshaped the understanding of ovarian cancer pathogenesis, particularly the role of genomic instability and DNA repair defects. Among the most critical discoveries is the involvement of BRCA1 and BRCA2 genes, which play essential roles in homologous recombination, a high-fidelity DNA repair pathway [4, 5]. Mutations in these genes compromise the cell's ability to repair double-strand DNA breaks, leading to genomic instability but also creating a therapeutic vulnerability. This vulnerability is exploited by PARP inhibitors, which target single-strand break repair mechanisms [6]. In tumors deficient in homologous recombination, inhibition of PARP leads to the accumulation of DNA damage and eventual cell death [7]. While this approach has revolutionized treatment, resistance inevitably develops, necessitating a deeper understanding of the underlying mechanisms.

2. BRCA Mutations in Ovarian Cancer

BRCA1 and BRCA2 are tumor suppressor genes that encode proteins critical for maintaining genomic stability [8-10]. Germline mutations in these genes are associated with hereditary breast and ovarian cancer syndrome, significantly increasing lifetime cancer risk [11, 12]. In ovarian cancer, approximately 15–20 percent of patients harbor germline BRCA mutations, while an additional subset exhibits somatic mutations [13-15]. BRCA1 is involved in DNA damage recognition and end resection, whereas BRCA2 facilitates the loading of RAD51 onto single-stranded DNA to promote

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strand invasion during homologous recombination [16, 17]. Loss of function in either gene disrupts accurate DNA repair, leading to chromosomal aberrations and tumorigenesis. Clinically, BRCA-mutated ovarian cancers tend to be more responsive to platinum-based chemotherapy due to their impaired DNA repair capacity [18-20]. This sensitivity also extends to PARP inhibitors, which have become a cornerstone in the maintenance therapy of these patients. However, not all BRCA mutations confer identical functional consequences. Variability in mutation type, location, and residual protein function can influence therapeutic response and resistance patterns [21]. Additionally, reversion mutations that restore BRCA function have been identified as a key mechanism of acquired resistance [22].

3. Homologous Recombination Deficiency Beyond BRCA

While BRCA mutations are the most well-characterized drivers of homologous recombination deficiency, a broader spectrum of genetic and epigenetic alterations can impair this pathway [23, 24]. These include mutations in genes such as RAD51C, RAD51D, PALB2, ATM, and CHEK2, as well as promoter methylation of BRCA1. The concept of "BRCAness" has been introduced to describe tumors that phenotypically resemble BRCA-mutated cancers despite lacking detectable BRCA mutations [25]. These tumors exhibit similar genomic scars, including loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions [26]. Diagnostic assays have been developed to quantify homologous recombination deficiency, enabling the identification of patients who may benefit from PARP inhibitor therapy beyond those with BRCA mutations [27-29]. However, the predictive accuracy of these assays remains an area of ongoing research. Importantly, homologous recombination deficiency is not static. Tumors can evolve under therapeutic pressure, leading to partial or complete restoration of DNA repair capacity. This dynamic nature complicates treatment decisions and underscores the need for longitudinal monitoring.

4. Mechanism of Action of PARP Inhibitors

PARP enzymes, particularly PARP1, play a crucial role in the repair of single-strand DNA breaks through the base excision repair pathway [30]. PARP inhibitors, such as olaparib, niraparib, and rucaparib, function by trapping PARP on DNA and preventing repair of single-strand breaks [31, 32]. During DNA replication, unrepaired single-strand breaks are converted into double-strand breaks. In cells with intact homologous recombination, these breaks can be accurately repaired. However, in homologous recombination-deficient cells, repair is error-prone or fails entirely, leading to cell death [33]. This concept of synthetic lethality forms the basis of PARP inhibitor therapy [34]. The selectivity of this approach allows for targeted killing of cancer cells while sparing normal cells with functional DNA repair mechanisms. Beyond PARP trapping, these inhibitors also modulate replication fork stability and influence chromatin remodeling [30, 35]. Differences in PARP trapping potency among various inhibitors may contribute to variability in clinical efficacy and toxicity [36, 37].

5. Mechanisms of PARP Inhibitor Resistance

Despite initial responses, many patients eventually develop resistance to PARP inhibitors [38]. Multiple mechanisms have been identified, often coexisting within the same tumor. One of the most prominent mechanisms is the restoration of homologous recombination through secondary or "reversion" mutations in BRCA genes [39]. These mutations restore the open reading frame and partially recover protein function, thereby rescuing DNA repair capability. Another mechanism involves the loss of proteins such as 53BP1, which normally antagonize homologous recombination [40]. Loss of 53BP1 shifts the balance toward homologous recombination, even in the absence of functional BRCA1 [41]. Replication fork protection has also emerged as a critical factor. Tumors can stabilize stalled replication forks, preventing their degradation and reducing reliance on homologous recombination [42]. Proteins such as PTIP and CHD4 are involved in this process. Drug efflux mechanisms, including upregulation of ABC transporters like P-glycoprotein, can decrease intracellular concentrations of PARP inhibitors, contributing to resistance [43]. Additionally, alterations in PARP itself, such as mutations that reduce drug binding or trapping efficiency, have been reported [44, 45].

6. Clinical Implications and Therapeutic Strategies

Understanding resistance mechanisms has led to the development of combination therapies aimed at overcoming or delaying resistance. Combining PARP inhibitors with agents that induce DNA damage, such as platinum chemotherapy or radiation, can enhance efficacy [46, 47]. Targeting complementary pathways has also shown promise. For example, inhibitors of ATR, CHK1, and WEE1 disrupt cell cycle checkpoints and increase replication stress, sensitizing tumors to PARP inhibition [35, 48]. Immune checkpoint inhibitors represent another avenue of investigation. Homologous recombination-deficient tumors often exhibit higher mutational burdens, potentially enhancing immunogenicity [49]. Early clinical trials suggest synergistic effects when PARP inhibitors are combined with immunotherapy [50]. Epigenetic

therapies, such as DNA methyltransferase inhibitors, may re-sensitize tumors by re-inducing homologous recombination deficiency [51]. Similarly, strategies to inhibit drug efflux or restore PARP trapping are being explored. Precision medicine approaches, including real-time genomic profiling and liquid biopsies, are increasingly important for guiding treatment decisions and monitoring resistance evolution.

7. Future Directions

The future of ovarian cancer treatment lies in understanding of tumor biology and adaptive resistance. Advances in single-cell sequencing and spatial transcriptomics are providing insights into tumor heterogeneity and microenvironment interactions. Biomarker development remains a priority. Identifying reliable predictors of response and resistance will enable better patient stratification and treatment optimization [52]. Functional assays that directly measure homologous recombination capacity may complement genomic approaches [27]. Novel agents targeting alternative DNA repair pathways are under investigation. These include inhibitors of DNA polymerase theta and other components of microhomology-mediated end joining. Ultimately, overcoming PARP inhibitor resistance will require integrated strategies that address the multifaceted nature of tumor evolution.

8. Conclusion

BRCA mutations and homologous recombination deficiency have fundamentally transformed the management of ovarian cancer, providing a rationale for targeted therapies such as PARP inhibitors. While these agents have significantly improved outcomes, resistance remains an inevitable challenge. A comprehensive understanding of the molecular mechanisms underlying resistance is essential for developing effective therapeutic strategies. Continued research into combination therapies, biomarker development, and tumor evolution will be critical for sustaining the clinical benefits of PARP inhibition and improving long-term survival in ovarian cancer patients.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflict of interest.

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