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Review Article

Role of BRCA1 and BRCA2 Mutations in the Molecular Genetic Mechanisms of Ovarian Cancer

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Abstract

Ovarian cancer is one of the most lethal oncological diseases among women, and hereditary factors play a crucial role in its pathogenesis. In this regard, the BRCA1 and BRCA2 genes are of particular importance as key tumor suppressor genes involved in the repair of DNA double-strand breaks through homologous recombination. Pathogenic mutations in these genes lead to disruptions in genome stability, the accumulation of DNA damage, and uncontrolled cell proliferation. As a result, the risk of developing ovarian cancer increases significantly. BRCA1 and BRCA2 gene mutations can be both hereditary (germinal) and somatic, and the spectrum of these mutations encompasses point mutations, insertion-deletion changes, and loss of large genomic segments. At the molecular-genetic level, these changes weaken DNA repair mechanisms and activate alternative, error-prone repair pathways. Recent studies have shown that ovarian cancer in BRCA mutation carriers has a different biological behavior and response to treatment; in particular, there is a high sensitivity to PARP inhibitors. For this reason, studying the molecular-genetic roles and mutation mechanisms of the BRCA1 and BRCA2 genes is of significant scientific and clinical importance for personalized diagnostics, risk assessment, and the development of targeted therapies.

Keywords: ovarian cancer, BRCA1 and BRCA2 genes, PARP inhibitor, DNA repair, gene mutation, targeted therapy

1. Introduction

Ovarian cancer is considered one of the most severe and complex oncological diseases of the female reproductive system and is characterized by high mortality rates. One of the main reasons for the danger of this disease is that clinical symptoms are non-specific or completely absent in the early stages. As a result, a large proportion of patients are diagnosed at late stages, which limits treatment options and reduces the likelihood of survival. Modern scientific research on the etiology and pathogenesis of ovarian cancer shows that not only environmental and hormonal factors, but also genetic and molecular mechanisms play a crucial role in the development of the disease [1].

Genetic predisposition is considered one of the most significant risk factors for the development of ovarian cancer. Mutations in the BRCA1 and BRCA2 genes, particularly within the framework of hereditary breast and ovarian cancer syndrome, necessarily increase the risk of developing the disease. These genes are tumor suppressor genes that perform necessary functions in maintaining the structural integrity of DNA in the cell, repairing damaged DNA sites, and regulating the cell cycle. Loss of their functional activity leads to disruption of genome stability and the creation of favorable conditions for malignant transformation [2].

In terms of molecular-genetic mechanisms, the BRCA1 and BRCA2 genes are mainly involved in the repair of DNA double-strand breaks through homologous recombination. This mechanism is considered one of the most reliable DNA repair pathways for the cell. However, when mutations occur in the mentioned genes, this

mechanism becomes ineffective, and the cell resorts to alternative, but more error-prone, repair pathways. Consequently, the mutation load increases, chromosomal abnormalities arise, and the process of tumor cell formation accelerates. In this regard, BRCA gene mutations are central to the molecular pathogenesis of ovarian cancer.

Mutations observed in the BRCA1 and BRCA2 genes can be germline (hereditary) and somatic in origin. Germline mutations are passed down from generation to generation, leading to an increase in familial ovarian cancer cases. Somatic mutations, on the other hand, arise later in tumor tissue and directly affect the course of the disease and response to treatment. The breadth of the mutation spectrum, including point mutations, insertions, and deletions, as well as large genomic rearrangements, suggests that functional loss of these genes can occur by various mechanisms [3].

In recent years, advances in molecular genetics and genomics have led to fundamental changes in the diagnostic and treatment strategies of ovarian cancer. Detection of BRCA mutations is of great importance for early screening of at-risk individuals, planning preventive measures, and implementing personalized treatment approaches. The introduction of targeted drugs, particularly PARP inhibitors, into clinical practice has led to improved treatment outcomes in BRCA mutation carriers. These drugs selectively target tumor cells by exploiting DNA repair deficiencies and have minimal effect on healthy cells.

Thus, studying the molecular-genetic role and mutation mechanisms of BRCA1 and BRCA2 genes in ovarian cancer is of significant scientific and practical importance not only in terms of understanding the biological basis of the disease, but also in clinical decision-making, assessing prognosis, and selecting effective treatment strategies. Systematic research on this topic will facilitate the development of oncogenetic approaches, the application of personalized medicine, and the formation of new perspectives in the fight against ovarian cancer.

2. Molecular-Genetic Mechanisms of BRCA1 and BRCA2 in Ovarian Cancer

Analysis of the molecular-genetic basis of ovarian cancer demonstrates that disturbances in DNA repair mechanisms play a crucial role in the development of the disease. In this context, the BRCA1 and BRCA2 genes are of particular importance as key tumor suppressor genes that maintain genome stability. Their functional loss leads to an increase in the accumulation of genetic damage in the cell, chromosomal instability, and, ultimately, malignant transformation.

In a healthy cell, the BRCA1 and BRCA2 genes ensure the high-fidelity repair of DNA double-strand breaks through homologous recombination. While BRCA1 is involved in damage recognition and recruitment of repair complexes, BRCA2 plays a role primarily in directing the RAD51 protein to the site of DNA damage. This interaction maintains the genetic integrity of the cell and ensures the normal continuation of the cell cycle [2].

A sister chromatid is one of two genetically identical copies of the same chromosome, formed by DNA replication before cell division. These two chromatids are joined together by the centromere and are separated and distributed to daughter cells during the processes of mitosis and meiosis. Mutations in the BRCA1 and BRCA2 genes cause loss of gene function through various molecular mechanisms. The most common types of mutations include:

- *Point mutations (missense and nonsense mutations)*
- *Insertions and deletions, resulting in frameshifting*
- *Large genomic deletions and duplications*

As a result of these mutations, the proteins synthesized are either completely dysfunctional or unable to participate in intracellular repair processes (Figure 1) [4]. In the end, the homologous recombination mechanism breaks down, and the cell resorts to inaccurate, error-prone alternative DNA repair pathways (e.g., non-homologous joining) [5].

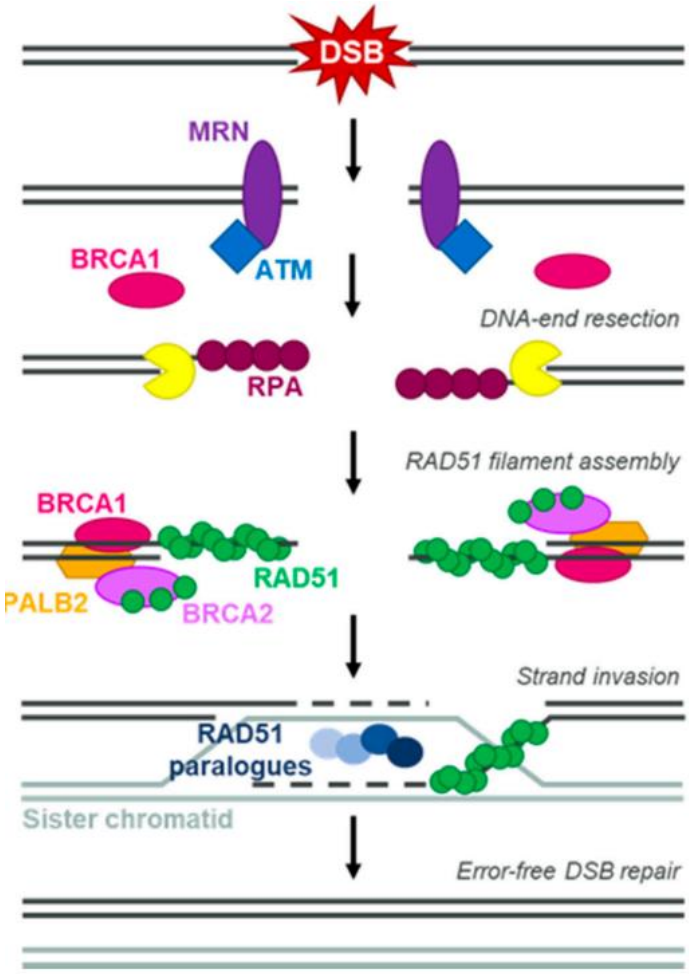


Figure 1. The error-free repair mechanism of DNA double-strand breaks via homologous recombination involving the BRCA1 and BRCA2 genes [4].

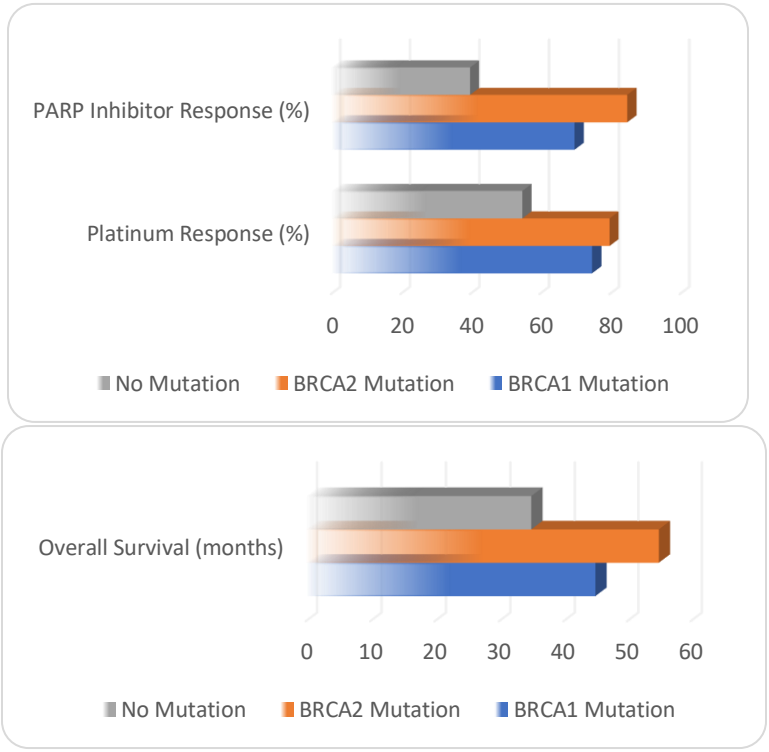
Table 1. Types of mutations in the BRCA1 and BRCA2 genes and their molecular-genetic and clinical consequences [6].

Mutation Type	Molecular Properties	Effect on BRCA Protein	Results at the Cellular Level	Relationship with Ovarian Cancer
Point mutations (missense)	Amino acid substitution resulting from a change in a single nucleotide	Partial impairment of protein function	Decreased efficiency of homologous recombination	Moderate risk increase
Nonsense mutations	Premature stop codon generation	Abbreviated and non-functional protein synthesis	Complete disruption of the DNA repair mechanism	High-risk, aggressive tumors
Insertions and deletions (frameshift)	Violation of the reading frame	Complete functional loss	Increased genomic instability	Strong link with hereditary ovarian cancer
Large genomic deletions	Loss of a large portion of the gene	Failure to synthesize the BRCA protein	Activation of error-prone DNA repair pathways	Early onset, high risk
Somatic mutations	Occurs only in tumor tissue	Local BRCA loss of function	Selective vulnerability in tumor cells	Hypersensitivity to PARP inhibitors
Germinal mutations	It is hereditary and present in all cells	Systemic BRCA deficiency	Chronic genomic instability	Familial risk of ovarian cancer

In Table 1, the main types of mutations observed in the BRCA1 and BRCA2 genes, their molecular-genetic characteristics, and the functional changes they cause at the cellular level are systematically presented [6]. The mutations shown here disrupt the structural and functional integrity of BRCA proteins through various mechanisms, reducing the efficiency of DNA repair through homologous recombination. Consequently, genomic instability occurs in cells, and favorable conditions are created for malignant transformation.

BRCA mutations in ovarian cancer are divided into two main groups based on their origin: germline and somatic mutations. Germline mutations are present in all cells and are considered the main genetic cause of hereditary breast-ovarian cancer syndrome. Carriers of such mutations have a significantly increased risk of ovarian cancer, and the disease can occur at an earlier age. Somatic mutations, on the other hand, form only in tumor tissue and are not hereditary. However, from a clinical perspective, these mutations are also necessary because they lead to loss of BRCA function and altered response to treatment. Studies have shown that patients with both germline and somatic BRCA mutations can have similar positive responses to targeted therapy [7].

BRCA mutation-associated ovarian cancer differs from classic sporadic cases in its molecular and clinical features. Such tumors have higher genomic instability, but at the same time, they are more sensitive to cytotoxic drugs and DNA-damaging therapies. Platinum-based chemotherapy in particular exhibits higher efficacy in patients with BRCA mutations. For example, clinical observations demonstrate that patients with BRCA1 mutations have a stronger initial response to treatment, but there is a risk of relapse. Patients with BRCA2 mutations have a relatively higher overall survival rate. These differences are explained by the specific roles of the BRCA genes in intracellular functions [3].



Graph 1. The effect of BRCA1 and BRCA2 gene mutations on clinical outcomes in ovarian cancer patients [8].

The impact of BRCA1 and BRCA2 gene mutations on treatment response and overall survival in ovarian cancer patients is presented comparatively. As can be seen from Graph 1, the response rate to platinum-based chemotherapy and PARP inhibitors is higher in patients carrying the BRCA1 and particularly BRCA2 mutations than in cases without the mutation. At the same time, patients with BRCA2 mutations have a relatively long overall survival time. These results explain the effectiveness of targeted therapies in relation to the role of BRCA genes in DNA repair mechanisms and form the scientific basis for personalized therapy approaches [8].

3. Clinical Implications and Targeted Therapeutic Approaches

Molecular genetic analysis of BRCA mutations has led to the development of new therapeutic approaches. The most significant of these approaches is the application of PARP inhibitors based on the principle of synthetic lethality. PARP proteins are involved in the repair of single-stranded DNA damage. Blocking the PARP pathway in cells with impaired BRCA function leads to a critical accumulation of DNA damage and tumor cell death. This mechanism is highly effective as a targeted therapy because it does not cause serious damage to healthy cells. Clinical trials reveal that disease-free survival is significantly prolonged in BRCA mutation-carrying ovarian cancer patients treated with PARP inhibitors [9].

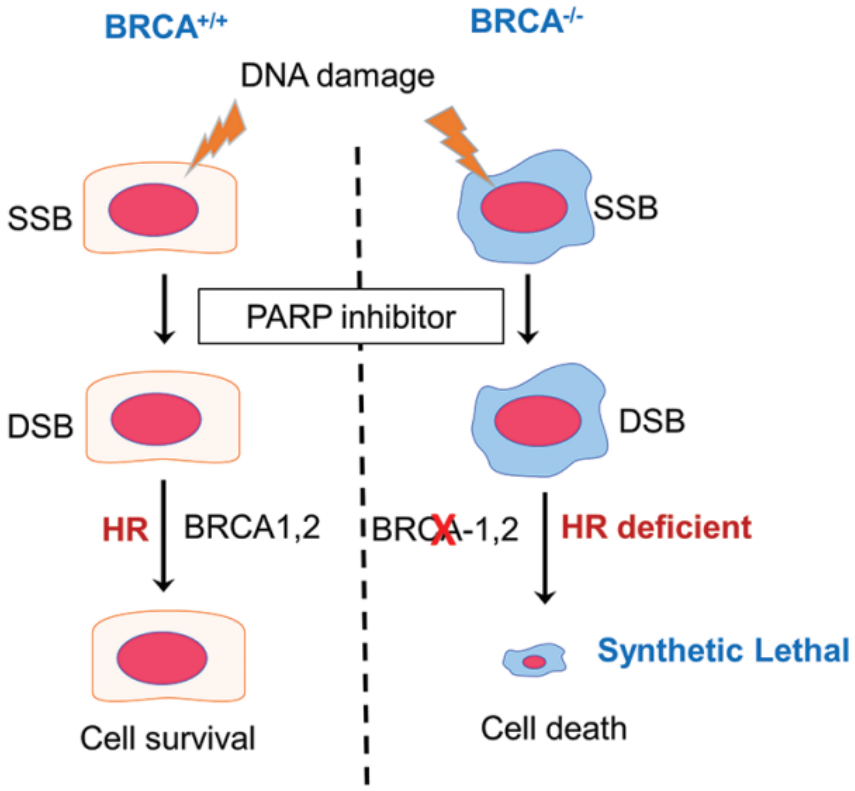


Figure 2. Synthetic lethality mechanism of PARP inhibitors depending on BRCA functional status [10].

The mechanism of action of PARP inhibitors in cells with normal BRCA function ($BRCA^{+/+}$) and cells carrying a BRCA mutation ($BRCA^{-/-}$) is shown comparatively in Figure 2 [10]. In $BRCA^{+/+}$ cells, DNA damage caused by PARP inhibitors is repaired by homologous recombination through BRCA1 and BRCA2, ensuring cell survival. Since $BRCA^{-/-}$ cells lack the homologous recombination mechanism, PARP inhibition causes single-stranded DNA lesions to become double-stranded breaks, and these lesions cannot be repaired. As a consequence, the accumulation of DNA damage at a critical level leads to cell death, a process characterized as the principle of synthetic lethality.

Molecular genetic analysis of the BRCA1 and BRCA2 genes plays a crucial role not only for treatment selection but also in risk assessment and identification of preventive strategies. The application of genetic tests allows for early monitoring of women at risk, planning of preventive surgical interventions, and establishing a personalized medical approach [11].

Thus, the analysis conducted shows that the role of BRCA mutations in ovarian cancer is not only pathogenetic, but also multifaceted in terms of clinical and therapeutic aspects. In-depth study of these genes at the molecular level makes a significant contribution to the development of oncogenetics, the improvement of modern oncological treatment strategies, and the improvement of the quality of life of patients.

4. Conclusion

The analysis demonstrates that the BRCA1 and BRCA2 genes play a central and decisive role in the formation of the molecular-genetic basis of ovarian cancer. These genes act as one of the main mechanisms in maintaining genome stability by ensuring error-free repair of DNA double-strand breaks through homologous recombination. Mutations in the BRCA1 and BRCA2 genes disrupt this protective mechanism, leading to the accumulation of genetic damage in cells, increased chromosomal instability, and ultimately the development of ovarian cancer.

Research results illustrate that BRCA mutations manifest in different forms due to their structural and functional properties, and both their germline and somatic variants are clinically necessary. While germline mutations are hereditary and contribute to the increased incidence of familial ovarian cancer, somatic mutations largely determine the biological behavior of the tumor and its response to treatment. These differences confirm that BRCA mutations have not only pathogenetic but also prognostic value.

Analyses conducted at the molecular-genetic level exhibit that BRCA functional deficiency leads to the formation of new approaches in modern oncological treatment. In particular, PARP inhibitors, based on the principle of synthetic lethality, significantly increase the effectiveness of targeted therapy by inducing selective cell death in BRCA-mutated ovarian cancer cells. Clinical observations reveal that patients with BRCA1 and particularly BRCA2 mutations have a more favorable response to treatment and overall survival rates.

Consequently, in-depth study of the molecular-genetic role and mutation mechanisms of the BRCA1 and BRCA2 genes is of significant scientific and practical importance in terms of early diagnosis of ovarian cancer, identification of risk groups, and implementation of personalized treatment strategies. Research in this area not only contributes to the development of oncogenetics but also allows for the development of more effective and targeted therapeutic approaches in the fight against ovarian cancer.

Author Contributions

The author confirms responsibility for the conception and final approval of the manuscript.

Conflict of Interest

The author declares no competing interests.

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Abbreviations

Breast Cancer 1 Gene (BRCA1), Breast Cancer 2 Gene (BRCA2), Deoxyribonucleic Acid (DNA), Double-Strand Break (DSB), Homologous Recombination (HR), Poly (ADP-ribose) Polymerase (PARP), PARP Inhibitor (PARPi), DNA Repair Protein RAD51 (RAD51), BRCA Wild-Type (Normal BRCA Function) ($BRCA^{+/+}$), BRCA Deficient / BRCA Mutated ($BRCA^{-/-}$), Ovarian Cancer (OC), Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Overall Survival (OS), Progression-Free Survival (PFS), Non-Homologous End Joining (NHEJ).

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