

# Controlling Relative miRNA level as Target Therapy of the BRCA Mutation and Its Challenges

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**Abstract.** In the past few decades, the diagnosis, prevention, and treatment of BRCA1/2-related cancer, especially breast cancer and ovarian cancer, have been a topic of great concern to scientists and the public. People with mutated BRCA genes are more likely to develop breast and ovarian cancer, and such causes of these types of cancer are inherited. Till now, there is no perfect solution for this gene defect. microRNAs (miRNAs), as important gene expression regulation molecules in humans, are considered to have the potential to be a tool for early diagnosis of such gene defects. In this review, the literature on miRNA closely related to BRCA gene regulation is reviewed, and the mechanism of miRNA causing BRCA gene variation is discussed. The online databases used in this research are PubMed, Nature Journals, ScienceDirect, The European Bioinformatics Institute (EBI), and Google Scholar. The search terms are “BRCA gene mutation”, “BRCA gene function”, “PARP inhibitor”, “miRNA for BRCA regulation”, “Target therapy for BRCA gene mutation”, “Drug resistance”, and “Target specificity”. This paper aims to discuss the possibility of reducing the incidence of BRCA gene mutation by controlling the content of relative miRNAs – reducing miRNAs that inhibit BRCA gene expression and increasing miRNAs that promote BRCA gene expression– and how to restore the function of the mutated BRCA gene by this means. The population that develops breast and ovarian cancer has been on the rise for decades, and the age of patients is getting younger. If miRNA can be developed as an early diagnostic tool, it will enhance the power of current cancer screening techniques and provide a more stable basis for early prevention and subsequent treatment.

**Keywords:** BRCA gene mutation; BRCA gene function; PARP inhibitor; miRNA for BRCA regulation; Target therapy for BRCA gene mutation; Drug resistance; Target specificity.

## 1. Introduction

The BRCA genes (BRCA 1 & BRCA 2) are known as cancer suppressor genes, reducing a person’s chance of developing breast cancer by repairing DNA breaks that can lead to that disease. Such a mechanism is called the “Homologous directed repair” (HDR) mechanism, working to repair double-strand breaks by exchanging DNA strands between a pair of homologous duplex DNA sequences. During the process, one strand acts as a template for the other strand to retrieve the missing or broken parts with the efforts of the BRCA protein.

The mutation in BRCA genes highly contributes to developing breast cancer, In the female population, this malignant tumor has the highest incidence and also has the second highest death rate among all kinds of cancers that can happen in women. The incidence rate of this cancer has been on the rise over the last couple of decades (about 0.5% per year) [1], and its prevention and treatment have been a topic of great concern to scientists and the public. People with families catching this mutated gene are more likely to have breast cancer. The prevalence rate can reach 50%-70% by the age of 70-80 compared to 13% for normal people [2]. Such a gene defect is found to be inherited, and so far there isn’t an efficient way to treat this mutation. The most used method is to do early screening and have preventive treatment (such as prophylactic mastectomy).

The miRNA works as a regulatory gene piece by binding certain parts of the DNA chain and therefore reducing their expression. It can contribute to the inactivation of BRCA genes, so miRNAs associated with breast cancer can be used as targets for early diagnosis or subsequent treatment. If the miRNA level can be controlled during the gene regulation, the lost BRCA gene functions may be restored.

## **2. Organization of the Text**

### **2.1. Technical Gaps of BRCA Gene Mutation Treatment**

The treatment of BRCA1&2-related cancers still relies on traditional cancer treatment - chemotherapy and radiation after surgery to remove the cyst. However, these two treatments have huge side effects that will massively destroy the patient's immune cells, causing the patient to suffer great pain, and even those in poor physical fitness cannot bear it and may not pass the treatment phase. For this reason, scientists have been searching for effective alternatives. Targeted cancer therapy is one of the most promising potential alternative treatments. However, the premise of targeted therapy is to find and accurately locate the corresponding molecular targets in cancer cells, which are important and identifiable molecules involved in the process of cancer cell formation and growth (such as receptor tyrosine kinases (RTKs) covering the surface of cancer cells) or molecular pathways. Only based on these targets, treatment is effective. However, BRCA1&2 gene mutations are highly heterogeneous, with multiple mutation types, each corresponding to specific gene function loss or damage, and involve many related regulatory genes, which may all become potential targets. The huge gene base increases the difficulty of finding truly effective targets, and this has been a major challenge in the development of targeted therapies for BRCA gene mutations.

Fortunately, scientists have made some achievements in the long search for effective targeted therapies for BRCA gene mutations, and one of the most promising research results is PARP inhibitors. In 2005, two research groups [3, 4] found that cells carrying BRCA gene mutations readily respond to the inhibitors of two molecules, Poly (ADP-ribose) polymerase 1&2 (they belong to a kind of DNA repair enzyme, and have an abbreviation of PARP 1&2).

This repair enzyme is mainly active in DNA when single-strand breaks (SSBs) occur and repair the broken or missing parts. Suppressing their levels leads to more SSBs and after replication, double-strand breaks (DSBs) occur. Using the principle of Synthetic lethality (SL), cells carrying BRCA variants will die under the influence of the combination of two defective genes. Cells that do not carry mutated BRCA genes will survive from PARP inhibitors through homologous recombination function, and achieve targeted therapy [5, 6].

However, PARP inhibitors have some defects such as excessive side effects, expensive price, and drug resistance. After PARP inhibitors entered the market, resistance was gradually observed, which may result from the influence of the tumor microenvironment. In particular, for cells in a specific cell cycle (G0, G1) [7], low responsiveness to inhibitors was observed, and this problem persists today. So far, despite many attempts by scientists, there is still huge room for improvement in effective targeted therapies for BRCA1&2-related cancers.

### **2.2. MiRNA-Based Targeted Therapy**

MicroRNAs (miRNAs) that target and regulate BRCA1&2 genes contribute to the onset and progression of cancer. These miRNAs indirectly affect the development of cancer by influencing the expression of BRCA genes. There are many miRNAs involved in BRCA regulation, and each miRNA has a different role, and the same miRNA can have multiple targets in cells. The most common miRNAs can be divided into two categories: miRNAs that inhibit BRCA gene expression and miRNAs that promote BRCA gene expression. Since BRCA is a tumor suppressor gene, reducing the content of miRNA that inhibits BRCA gene expression or enhancing the miRNA that promotes BRCA gene expression can achieve the purpose of treating BRCA gene mutations. Here are some examples of miRNAs that are known to interact with BRCA genes:

Common miRNAs that inhibit BRCA gene expression include miR-182 [8], which is an miRNA targeting BRCA1, and excessive content of Mir-182 will lead to the suppression of BRCA1 expression, thereby increasing the incidence of breast cancer and ovarian cancer; miR-155 [8], an miRNA that targets both BRCA1 and BRCA2, is closely related to breast cancer caused by BRCA

gene mutation; miR-146a [8], which targets the BRCA1 gene, is considered one of the causes contributing to breast cancer susceptibility.

Common miRNAs that promote BRCA gene expression include miR-638 [8], targeting BRCA1 inhibitors and reducing their expression, therefore, it has the potential to restore the function of the mutated BRCA1 gene and gives a good inhibitory effect on breast cancer caused by BRCA gene mutation; miR-146a and miR-182 [8], the two miRNAs mentioned above which can inhibit the expression of BRCA1, are in fact involved in multiple gene regulation processes. Especially at the level of molecular pathways, they have inhibitory effects on cancer, which also proves the complexity of potential targets. At this point, miR-146a and miR-182 may not be good choices for molecular targets, because they affect the occurrence and development of cancer in nonmonotonic ways, and they are also affected by the cellular microenvironment. It is difficult to achieve the targeted therapeutic effect of cancer suppression by simply controlling their content.

One thing worth considering is that even for miRNAs involved in only a few regulations, the regulatory process is extremely complex and susceptible, and various small factors in different scenarios may change the influence of specific miRNAs on BRCA gene expression, so it is necessary to pay attention to specific situations when selecting targets.

### **2.3. Ensure that miRNA-based therapies are specific for BRCA mutated cancer cells**

When developing a drug or method for targeted therapy, it is important to minimize damage to healthy cells and avoid off-target effects. This requires that miRNA-based target therapies have extremely high precision in the targeting specificity held by BRCA-mutated cancer cells. To achieve this, many assays and analyses are needed to identify targets for specific miRNAs in cells.

To improve the specificity, at first, a comprehensive miRNA spectrum analysis needs to be conducted on the cells of patients (including normal cells and BRCA mutant cancer cells). This step is to find out the miRNAs that are different from normal cells in cancer cells, and these miRNAs may be abnormal in content or function, thus negatively affecting the expression of genes. At the same time, these miRNAs will also serve as candidate targets for targeted therapy. Repeated verification until the selection of miRNA confirmed to have a biologically relevant effect on various activities of cancer cells, as a target. Through the type of action of the miRNA on the BRCA gene, reagents can be designed to control the target content towards the expected value, a step that is key to enhancing specificity. After this step is completed, the targeted therapeutic drug has taken shape, and the subsequent need to consider how to deliver it to the cancer cell, micro-materials such as nanoparticles, and liposomes can be chosen, or treated viral vectors, which can complete the targeted delivery process. In the process of delivery, it is necessary to strictly ensure that the delivery target is the selected cancer cells, otherwise, it is easy to appear off-target effect.

In addition, combining miRNA-based targeted therapy with other types of targeted therapy to complement each other can also effectively improve specificity.

### **2.4. Resistance of cancer cells to miRNA-based therapies**

Resistance to targeted therapies has been a common and serious problem. With PARP as a precedent, special attention should be paid to various cellular mechanisms that may cause drug resistance when developing targeted therapies for BRCA gene mutations. For example, two teams of researchers [9] have found that a secondary mutant BRCA2 gene will cause cells to the drug resistance of PARP inhibitors other studies have suggested that P53BP1 expression loss will also make the cells resistant [10].

Therefore, in the development process of targeted therapy and the initial stage of use, it is necessary to monitor patients intensively for a long time to determine whether the treatment effect is gradually declining.

### 3. Conclusion

Targeted therapies for cancer-causing BRCA mutations typically focus on restoring normal BRCA gene function or inhibiting the growth of cancer cells with these mutations. While regulating microRNA (miRNA) levels is a potential area of research for targeted therapies in cancer, it is also a complex and evolving area with many challenges. In future studies, it will be necessary to closely monitor whether this potential treatment is specific for inhibiting cancer cells and minimizing the possibility of developing resistance.

The development of therapies to treat BRCA gene mutations by controlling the content of miRNA fragments that inhibit BRCA gene expression can reduce the difficulty of cancer treatment, and even replace surgery and chemotherapy to a certain extent, making the treatment process of patients less painful. A good wish is that in the future, miRNA-based targeted therapies will be developed to allow patients to endure the least pain, obtain the best treatment results, and strengthen the entire human science for the prediction, prevention, and treatment of related cancers caused by BRCA mutations.

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