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A Review of the Research on DNA Methylation Mediated Epigenetic Remodeling of HRD and Immune Microenvironment in Acquired Resistance to PARP Inhibitors in Ovarian Cancer

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ABSTRACT

Adenosine diphosphate ribose polymerase (PARP) inhibitors have become an important targeted therapy for ovarian cancer patients carrying homologous recombination repair defects (HRD), but acquired resistance severely limits the long-term benefits of PARP inhibitors. Recent studies have shown that epigenetic remodeling mediated by DNA methylation plays an important role in the resistance process of PARP inhibitors. Therefore, in addition to inducing HRD phenotype reversal by silencing homologous recombination repair related genes, it can also synergistically mediate drug resistance by regulating the tumor immune microenvironment. This article reviews the epigenetic reversal of HRD and its impact on the immune microenvironment in ovarian cancer PARPi acquired resistance through DNA methylation. This article further introduces the application prospects, existing problems, and future prospects of demethylation drugs combined with PARP inhibitors or immunotherapy for DNA methylation, providing a new theoretical basis and possible approaches for solving clinical drug resistance.

KEYWORDS

Ovarian cancer; PARP inhibitors; Acquired resistance; DNA methylation

1. INTRODUCTION

Ovarian cancer is one of the deadliest gynecological malignancies. The homologous recombination repair defect (HRD) state is caused by mutations in the BRCA1/2 gene or other genes. These tumors are highly sensitive to PARP inhibitors (PARPi) and have become the basis and prerequisite for the application of PARPi. PARPi can specifically kill tumor cells by exerting a "synthetic lethal" effect on HRD tumors, significantly improving the PFS time of advanced ovarian cancer patients; However, the emergence of drug resistance over time severely restricts its clinical application effectiveness [1].

Early research mainly focused on genetic factors such as second round gene mutations caused by drug resistance, upregulation of drug efflux transporters, or HR recovery. However, an increasing number of recent studies suggest that epigenetic changes, especially DNA methylation modifications, can significantly affect gene and cell functions without causing DNA sequence variations, and play an important role in the evolution of tumors and treatment resistance. DNA methylation is one of the important epigenetic modifications on DNA, generally referring to the process of adding a methyl group to cytosine nucleotides (CpG dinucleotides) catalyzed by DNA methyltransferases (DNMTs). High methylation of the promoter region can cause transcriptional silencing of genes, and abnormal DNA methylation often occurs in tumors.

This article mainly focuses on DNA methylation as one of the important epigenetic modifications that play a role in PARPi acquired resistance in ovarian cancer. It summarizes two aspects: affecting

the occurrence and development of HRD in tumor cells and indirectly regulating the tumor immune microenvironment. It also briefly discusses the application prospects and research bottlenecks of comprehensive treatment models targeting DNA methylation [2]. We hope that this study can provide new ideas for understanding and overcoming PARPi resistance.

2. ACQUIRED RESISTANCE TO PARP INHIBITORS: FROM HRD DEFICIENCY TO EPIGENETIC PERSPECTIVE

At present, the mechanisms of acquired resistance to PARPi are diverse. The classic mechanisms include: (1) restoration of HR function, including secondary mutations in the BRCA1/2 gene or abnormalities in other genes involved in HR (RAD51C/D, PALB2), leading to a reversal of the previously observed HRD phenotype; (2) Enhancement of replication fork protection by upregulating proteins such as MRE11 and CHD4 to stabilize stagnant replication forks and reduce the use of PARPi; 3) Overexpression of drug efflux pumps (such as P-gp) reduces intracellular drug concentration. These mechanisms of action are mostly changes in gene sequence or direct regulation of protein function [3].

However, both clinical and preclinical studies have found that certain drug-resistant tumors do not exhibit significant genetic mutations related to HR function recovery, indicating the existence of an intangible drug resistance pathway. Among them, epigenetic regulation, especially DNA methylation, has received widespread attention. Unlike irreversible gene mutations, DNA methylation is a dynamic and reversible modification process that can rapidly and flexibly alter the cellular transcriptome to adapt to therapeutic stress. A study has found that when PARPi acts on tumor cells for a long time, there is selection pressure. Tumor cells can rapidly silence HR pathway related genes (such as BRCA1 and RAD51C) through high methylation in the promoter region, which can simulate a phenotype of HR function recovery even without changing their genetic background, also known as "epigenetic HRD reversal". This also expands the perspective of drug resistance research from simply lacking a certain gene level to a larger category that includes active epigenetic reshaping.

3. THE CORE ROLE OF DNA METHYLATION MEDIATED EPIGENETIC REMODELING IN PARPI RESISTANCE

DNA methylation plays a key role in PARPi resistance drive by directly affecting the expression of DNA damage repair related genes. The specific mechanisms are described below.

The first and most direct method is to directly silence homologous recombination repair genes, leading to HRD phenotype reversal. There are literature reports that in some acquired drug-resistant ovarian cancer models, the promoter region of the BRCA1 gene is highly methylated, causing transcription obstruction and protein inability to express [4]. This epigenetic silencing is functionally equivalent to an inactivated mutation, restoring the homologous recombination repair ability of tumor cells and thus tolerating DNA damage caused by PARPi. In addition to BRCA1, key genes in other HR pathways such as RAD51C and FANCF have also been reported to be inactivated and cause clinical drug resistance due to high promoter methylation. The upregulation or abnormal activation of DNA methyltransferases (DNMTs) such as DNMT1 and DNMT3B is the key enzymatic basis that drives this process.

Secondly, DNA methylation can widely affect other DDR pathways and reshape the repair network of cells. Gene silencing caused by high methylation of the MMR gene MLH1 promoter is also a characteristic of cellular response to DNA damaging agents in Lynch syndrome and some sporadic tumors. Although it is generally believed that the relationship between MMR defects and PARPi sensitivity is complex, this also suggests that methylation regulates DDR networks at multiple levels [5]. Moreover, genes related to replication fork stability and base excision repair may also be

regulated by methylation, thereby jointly forming a repair landscape conducive to cell survival under PARPi pressure.

Finally, this epigenetic remodeling is global and malleable. Drug resistant cells not only undergo methylation changes on certain repair genes, but also reshape the entire methylation and transcriptome. And such reprogramming endows tumor cells with strong adaptability, allowing them to transition from a state dependent on one pathway (such as HR) to a state dependent on other survival pathways. The methylation of DNA is reversible, so by removing the pressure of relevant treatments or combining other DNA demethylating agents, this resistance phenotype may be reversed, providing a potential clinical solution.

4. THE IMPACT OF EPIGENETIC REMODELING ON THE TUMOR IMMUNE MICROENVIRONMENT

In addition to its impact on tumor cells themselves, PARPi can also activate natural immune signals (including cGAS STING) by causing DNA damage and genomic instability, enhancing tumor immunogenicity and producing synergistic effects with immune checkpoint inhibitor [6]. However, epigenetic reprogramming mediated by DNA methylation equally affects the tumor immune microenvironment, which is another aspect of PARPi resistance.

4.1. Methylation Related Gene Silencing and Changes in Tumor Antigen Presentation

DNA methylation can silence genes involved in antigen presentation, allowing tumor cells to evade immune surveillance and play a role during the escape phase of tumor immune editing. The high methylation of the coding gene promoters of major histocompatibility complex class I molecules and related antigen processing transporters has been shown to be a pathway for many tumor immune escape. This epigenetic change is most worthy of attention in ovarian cancer, as it directly affects the specific and cytotoxic recognition of tumor by cytotoxic T lymphocytes.

In particular, full length MHC class I antigen presenting pathway plays a vital role in immunity process which includes several processes like generation of antigenic peptides,transport, loading, and surface presentation, all of which are regulated and controlled by relevant genes.It was shown, that the functional defectiveness of the antigen peptide transporters expressed by the TAP1 / TAP2 genes leads immediately to the inability of transporting endogenous antigenic peptides from the cytoplasm into the ER cavity,thus influencing the antigen loading of MHC-I molecules. β 2-microglobulin is a stable part of MHC-I molecules, and methylation of these genes that they encode could also result in downregulation of the cell surface expression of MHC-I molecules.The CpG island on the promoter region of the above key gene has been highly methylated and can stably inhibit its transcriptional activity for a long time,leading to immune escape at the epigenetic level [7].

In the context of PARPi acquired resistance in ovarian cancer, this epigenetic change may have a dual double check advantage: previous studies have shown that under long-term PARPi selection pressure, tumor cell clones can evolve towards different escape mechanisms; However, functional defects in the MHC-I class molecular antigen presentation pathway enable tumor cells to evade the increased genomic instability that exposes their new antigens to the body's immune system. That is to say, the synthetic lethal effect of PARI killing tumor cells may complement the negative effect of selectively enriching subclones with dual characteristics of DNA repair gain and immune escape phenotype. Researchers have found cases of low tumor mutation burden and new antigen count in ovarian cancer after PARPi resistance in clinical practice, suggesting that it may be due to selective pressure caused by antigen presentation dysfunction.

4.2. Reshaping of Immunosuppressive Microenvironment

DNA methylation has a wide range of regulatory effects on the establishment of tumor immune suppressive microenvironment, including the immune changes of tumor cells themselves and the regulation of the functions of various immune cells in the tumor microenvironment [8]. In ovarian cancer PARPi acquired resistance, therefore, this epigenetic mediated microenvironment reprogramming may be a supportive niche for promoting survival resistant clones.

In addition, tumor cells can suppress the transmission and amplification of immune signals from the source by silencing genes related to the IFN response pathway through high methylation. The functional integrity of the IFN pathway, as a key hub connecting innate and acquired immunity, is crucial for the formation of effective anti-tumor immune responses [9]. The resistance mechanism of tumor cells to antibody antibody dependent cytotoxicity after high promoter methylation of IFN α/β receptor or IFN γ receptor encoding genes leads to low expression: tumor cells lose sensitivity to interferon signals produced by immune cells, thus unable to effectively induce the expression of MHC class I molecules, and also lead to a decrease in sensitivity to immune effector molecules (including granzyme and perforin).

More importantly, defects in the interferon signaling pathway can reduce the production of chemokines, indirectly affecting the recruitment and infiltration of immune cells to the tumor site.

In addition, the impact of methylation regulatory networks on the expression of immune checkpoint molecules is also worth our attention. The inactivation of certain tumor suppressor genes, such as the TET family of DNA methylation inhibitors or the methylation silencing of certain microRNA genes, can indirectly lead to upregulation of PD-1 or PDL-1 expression through complex regulatory networks. This epigenetic change creates a dilemma in the microenvironment: tumor cells reduce their ability to present antigens themselves while increasing their inhibitory effect on T cells, allowing drug-resistant tumor clones to survive to the fullest extent possible with the help of the immune system.

The tumor cells release abnormally methylated DNA fragments and nucleosomes as important signaling molecules to regulate the microenvironment. They carry epigenetics,they can be recognized by PRRs present on TAMs and MDSCs to promote conversion of TAMs/MDCS toward an M2/inhibitory phenotype.which is primarily done by activation of downstream pathways, such as NF kB via the Toll like receptor 9 signaling pathway,stimulating the secretion of immunosuppressive cytokines (e.g., interleukin-10, transforming growth factor β), which creates a positive feed-backloop: tumor cells carrying an epigenetic disorder constantly secrete these signaling molecules in order to drive and maintain a powerful immunosuppressive microenvironment,which, in turn, helps the tumour cells to resist.They are attacked by the immune system. Make an environment of safety for them, where they will become therapeutic pressure.

4.3. Epigenetic Regulation of Immune Cell Infiltration and Function

In addition to controlling gene expression within a tumour cell, epigenetics can affect the function of infiltrating immune cells in the tumour microenvironment which might itself be controlled by the tumour cell's methylation pattern .For instance, T cell dysfunction has been associated with a fixed remodeling of the T cell epigenome (mostly HMs) ,but recent research indicates that tumoral global hypomethylation or methylation of some factors can influence, indirectly, the process of T cells differentiation and function by secretions of cytokines. Also,DNMT inhibitors also enhance the anti-tumor activity of T and NK cells.Thus, the methylation group remodeling in response to PARPi resistance might establish a suppressive immune niche enabling the expansion of drugresistant cells through changing the secretion group or cell-cell communication of tumour cells,remotely reprogrammed the functionality of immune cells.

5. STRATEGIES AND CHALLENGES FOR TARGETED EPIGENETIC REVERSAL OF DRUG RESISTANCE

Due to the important role that DNA methylation plays in PARPi resistance and because it is reversible, targeted DNA methylation is an increasingly popular way to overcome resistance.

5.1. Combination Therapy of Demethylating Drugs and PARPi

Demethylating drugs such as azacitidine and decitabine can integrate into DNA, irreversibly bind and inhibit DNMTs, causing overall DNA hypomethylation and reactivation of genes silenced by high methylation. Preclinical studies have confirmed that low-dose decitabine or azacitidine can reverse methylation silencing of genes such as BRCA1 in ovarian cancer models, restore their expression, and partially restore tumor sensitivity to PARPi. In addition, this type of combination may produce synergistic effects, restoring HR gene expression and reversing HRD phenotype, while also increasing tumor immunogenicity by restoring the signaling pathways of tumor antigens and IFN [10]. Currently, multiple clinical trials combining PARP i with DNMTi are underway for the treatment of recurrent ovarian cancer, which is expected to bring new treatment methods to drug-resistant patients.

5.2. Synergistic Effect of Epigenetic Therapy and Immunotherapy

As mentioned earlier, demethylating drugs themselves are immune modulators. Therefore, the triple therapy of PARPi+demethylating drugs+ICs (such as anti-PD-1/PD-L1 antibodies) has also attracted much attention. The logical basis is that PARPi causes DNA damage and immunogenicity; Demethylating drugs reverse immune related gene silencing, increase antigen presentation and interferon signaling, and may reverse HRD phenotype; And immune checkpoint inhibitors relieve the inhibitory effect of activating T cells. This multi pronged strategy will simultaneously target the repair ability, immune escape ability, and immune suppression in the microenvironment of tumor cells, potentially producing potent synergistic anti-tumor effects and overcoming resistance mediated by a single mechanism.

5.3. Exploration of Biomarkers and Patient Stratification

However, this joint operation is still challenging. The first step is how to find suitable biomarkers to select potential beneficiaries. Not all PARPi resistance is driven by DNA methylation, nor are all tumors responsive to demethylating drugs. One of the future research directions is to search for methylation biomarkers that can predict therapeutic effects, such as the methylation status of specific genes (such as BRCA1, RAD51C) promoters, whole genome methylation patterns, or methylation patterns related to the immune microenvironment. In addition, controlling the toxic side effects of combination therapy, especially triple therapy, is an important aspect that cannot be ignored in clinical practice; How to arrange the sequence, dosage, and timing of medication, and find a balance between effectiveness and safety. This is the key to successful conversion.

6. CONCLUSION

The epigenetic remodeling mediated by DNA methylation is one of the important and malleable mechanisms of PARPi acquired resistance in ovarian cancer. It can cause functional reversal of HRD phenotype in tumor cells by directly silencing HR related repair genes, and can extensively reshape the tumor immune microenvironment, inhibit antigen presentation, and promote immune suppression. From another perspective, it provides a shelter for the survival of drug-resistant tumor cells. The above two pathways do not exist in isolation, but are interconnected to form a complex network of drug resistance, which will elevate the understanding of drug resistance from static genetic defects to dynamic epigenetic immune microenvironment interactions.

In summary, demethylating drugs targeting DNA methylation are a new tool for reversing chemotherapy resistance, and their combination with PARP i or immunotherapy may help overcome multiple resistance mechanisms. There are still many areas worth exploring how to translate theory into clinical practice, such as precise selection of biomarkers, reasonable combination methods, and treatment of superimposed toxicity. In summary, further research in the future needs to combine multiple omics methods to explore the co evolution process between tumor epigenetic gene regulation and immune microenvironment under PARPi pressure at more precise and quantitative spatial and temporal scales, and provide a basis for better personalized combination therapies to improve the prognosis of ovarian cancer patients.

REFERENCES

[1] Queenie Chen, Jigme P Dorji, SandaliG Perera, Petvy Li, Fizza Aijaz, Linda C Ihuoma, Hiroshi Matsui, Chidiebere U Awah. In vivo inhibition of c-MYC in the metastatic drug-resistant ovarian cancer cells down regulates the c-MYC-PD-L1-PAX8-p21 to achieve therapeutic efficacy [J]. BMC cancer, 2025, 26 (1): 68-68.

[2] Hiroyuki Yoshida, Jiarui Li, Hiroaki Inui, Kyuji Rokugawa, Keiichi Fujiwara. RECQL1 as a potential therapeutic target for PARP inhibitor-resistant ovarian cancer [J]. Scientific Reports, 2025, 15 (1): 38089-38089.

[3] Liu Chaohua, Li Jiana, Xu Fei, Chen Lihua, Ni Mengdong, Wu Jiangchun, Zhao Haiyun, Wu Yangjun, Li Jiajia, Wu Xiaohua, Chen Xiaojun. PARP1-DOT1L transcription axis drives acquired resistance to PARP inhibitor in ovarian cancer [J]. Molecular Cancer, 2024, 23 (1): 111-111.

[4] Wethington Stephanie L, Shah Payal D, Martin Lainie, Tanyi Janos L, Latif Nawar, Morgan Mark, Torigian Drew A, Rodriguez Diego, Smith Simon A, Dean Emma, Domchek Susan M, Drapkin Ronny, Shih IeMing, Brown Eric J, Hwang WeiTing, Armstrong Deborah K, Gaillard Stephanie, Giuntoli Robert, Simpkins Fiona. Combination ATR (ceralasertib) and PARP (olaparib) Inhibitor (CAPRI) trial in acquired PARP-inhibitor-resistant homologous recombination deficient ovarian cancer [J]. Clinical cancer research: an official journal of the American Association for Cancer Research, 2023, 29 (15):

[5] Sauriol Alexandre, Carmona Euridice, Udaskin Molly L, Radulovich Nikolina, LeclercDesaulniers Kim, Rottapel Robert, Oza Amit M, Lheureux Stephanie, Provencher Diane M, MesMasson AnneMarie. Inhibition of nicotinamide dinucleotide salvage pathway counters acquired and intrinsic poly (ADP-ribose) polymerase inhibitor resistance in high-grade serous ovarian cancer [J]. Scientific reports, 2023, 13 (1): 3334-3334.

[6] Perez Fidalgo J.A., Sanchez-Serrano P., Heredia V., Martinez Pretel J.J., Hochstadt J., Mendiola M., Redondo Sanchez A., Burgués O., Pineda Merlo B. 585P Trabectedin induces apoptosis regardless of acquired resistance to PARP inhibitors in BRCA2 mutant high grade ovarian cancer cell lines [J]. Annals of Oncology, 2022, 33 (S7): S814-S814.

[7] Nesic Ksenija, Kondrashova Olga, Hurley Rachel M, McGehee Cordelia D, Vandenberg Cassandra J, Ho GwoYaw, Lieschke Elizabeth, Dall Genevieve, Bound Nirashaa, ShieldArtin Kristy, Radke Marc, Musafer Ashan, Chai Zi Qing, Eftekhariyan Ghamsari Mohammad Reza, Harrell Maria I, Kee Damien, Olesen Inger, McNally Orla, Traficante Nadia, Cancer Study Australian Ovarian, DeFazio Anna, Bowtell David D L, Swisher Elizabeth M, Weroha S John, Nones Katia, Waddell Nicola, Kaufmann Scott H, Dobrovic Alexander, Wakefield Matthew J, Scott Clare L. Acquired RAD51C promoter methylation loss causes PARP inhibitor resistance in high grade serous ovarian carcinoma [J]. Cancer research, 2021, 81 (18): 4709-4722.

[8] Wethington Stephanie L., Shah Payal D, Martin Lainie P., Tanyi Janos Laszlo, Latif Nawar A., Morgan Mark Aloysuis, Torigian Drew A., Pagan Cheyenne, Rodriguez Diego, Domchek Susan M., Drapkin Ronny, Shih Ie Ming, Smith Simon, Dean Emma, Armstrong Deborah Kay, Gaillard Stephanie, Simpkins Fiona. Combination of PARP and ATR inhibitors (olaparib and ceralasertib) shows clinical activity in acquired PARP inhibitor-resistant recurrent ovarian cancer [J]. Journal of Clinical Oncology, 2021, 39 (15S): 5516-5516.

[9] Kondrashova Olga, Nguyen Minh, Shield-Artin Kristy, Tinker Anna V, Teng Nelson N H, Harrell Maria I, Kuiper Michael J, Ho Gwo-Yaw, Barker Holly, Jasin Maria, Prakash Rohit, Kass Elizabeth M, Sullivan Meghan R, Brunette Gregory J, Bernstein Kara A, Coleman Robert L, Floquet Anne, Friedlander Michael, Kichenadasse Ganessan, O'Malley David M, Oza Amit, Sun James, Robillard Liliane, Maloney Lara, Bowtell David, Giordano Heidi, Wakefield Matthew J, Kaufmann Scott H, Simmons Andrew D, Harding Thomas C, Raponi Mit. Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma [J]. Cancer discovery, 2017, 7 (9): 984-998.

[10] K. Lin, A.V. Tinker, O. Kondrashova, G. Ho, M. Wakefield, R.L. Coleman, D.M. O'Malley, A. Floquet, J. Sun, L. Maloney, H. Giordano, T. Harding, M. Raponi, I.A. McNeish, E. Swisher, C.L. Scott. Secondary mutations in RAD51C and RAD51D are associated with acquired resistance to the PARP inhibitor rucaparib in patients with high-grade ovarian cancer [J]. European Journal of Cancer, 2016, 69 (S1): S13-S13.