WEP Warwick Evans Publishing

International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 5, Number 1, Year 2025
DOI: https://doi.org/10.62051/ijphmr.v5n1.01
Journal homepage: https://wepub.org/index.php/IJPHMR/index

The Role of Epigenetic Factors in Cancer Drug Resistance

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ABSTRACT

Cancer is one of the major global health threats. In cancer treatment, the development of drug resistance and tumor recurrence are important clinical challenges. Epigenetic regulation is closely associated with the occurrence and progression of cancer, and many recent studies have also shown that abnormal epigenetic regulation is widely linked to cancer drug resistance. This article reviews the impact of various abnormal epigenetic modifications on cancer drug resistance and discusses the potential of combining epigenetic drugs with existing cancer treatment methods to overcome cancer drug resistance.

KEYWORDS

Epigenetics; Cancer; Drug Resistance

1. INTRODUCTION

Cancer ranks among the top causes of death in the humans. Globally, nearly 10 million people die from cancer each year, among which more than 2 million deaths occur in China annually. The mainstream cancer therapy methods encompass chemotherapy, radiation therapy, surgical intervention, molecularly targeted therapy, and immune-oncology therapy. Although cancer treatment methods continue to advance with the exploration of new mechanisms and the emergence of new technologies, the development of cancer drug resistance still plagues patients and doctors.

Cancer drug resistance develops through a complicated and ever-changing process, often resulting from the interaction of multiple innate and acquired factors. Cancer treatment resistance was first observed in the 1940s during studies on hematological neoplastic diseases [1]. From the earliest research on chemotherapy drug resistance to the exploration of targeted molecular pathways and their clinical applications, research on cancer drug resistance has made considerable progress so far. Currently, it is generally believed that the causes of cancer drug resistance include tumor heterogeneity, DNA damage and repair mechanisms, genetic and epigenetic mechanisms, tumor microenvironment and tumor immunity, as well as epithelial-mesenchymal transition. We focus on the epigenetic mechanism among these factors. Epigenetics refers to a phenomenon where heritable changes in gene expression levels occur without changes in the gene sequence, through various modifications and regulatory effects. Many current studies have shown that epigenetic dysregulation is not only a key factor in carcinogenesis but also an important cause of tumor drug resistance.

2. EPIGENETIC REGULATION

In reaction to diverse environmental stimuli, Mammalian cells have formed complex epigenetic and transcriptional mechanisms, which serve to align gene expression and control the functions of cells [2]. Epigenetics pertains to alterations in the epigenome, rather than the genome itself, which include how chromatin undergoes chemical changes (through DNA and histone modifications) or structural

changes (through chromatin remodeling and interchromosomal/intrachromosomal DNA-DNA/protein interactions) [3]. Currently, the main mechanisms of epigenetic regulation involve covalent modifications, including histone modifications, DNA methylation, RNA modifications, and non-coding RNAs (ncRNAs) [4]. These epigenetic patterns are inherently related to the occurrence, progression, and treatment of tumors.

DNA methylation, a process typically facilitated by DNA methyltransferases (DNMTs), s-adenosylmethionine (SAM) provides a methyl group to replace the hydrogen on the 5'-carbon of cytosine in CpG dinucleotides, forming 5-methylcytosine (5mC). It is the most well-studied epigenetic modification. This type of modification has the capacity to trigger variations in DNA stability, DNA conformation, chromatin structure, and DNA–protein interplay, which in turn exerts a regulatory impact on the process of gene transcription [4]. Due to its regulatory effect on DNA transcription, DNA methylation is essential to a wide variety of biological pathways, which include aging, tumorigenesis, and the emergence of diseases [5].

Histone modification plays a crucial role as a regulatory mechanism in the field of epigenetics. What allows it to regulate gene expression and chromatin structure is the addition or removal of specific chemical substituents on histones [6]. Methylation, phosphorylation, acetylation, and ubiquitination are the types of histone modifications that have been relatively well studied, while lactylation, crotonylation, glycosylation, and citrullination are newly discovered in recent studies. The histone modifications also play a vital role in preserving the stability of chromatin structure and governing DNA replication, transcription, and repair, are strongly correlated with the emergence and progression of numerous types of cancer [7].

Chromatin remodeling complexes, such as SWI/SNF or BAF/PBAF, among others, utilize the energy derived from ATP hydrolysis to move nucleosomes or alter the relationship between histones and DNA, therefore the gene accessibility and expression are controlled [8]. Chromatin remodeling mechanisms also play an important role in the occurrence and development of tumors.

Non-coding RNAs (ncRNAs) are defined as a group of RNAs that fail to encode proteins. They are important components of the transcriptome and perform key regulatory functions in many cellular pathways through post-transcriptional regulatory processes. They have a significant impact on gene translation and transcription, cell senescence, cell differentiation, cell proliferation, cell death, as well as genetic and epigenetic pathways [9].

3. EPIGENETIC REGULATION AND TUMOR DRUG RESISTANCE

(1) DNA Methylation

Abnormal DNA methylation is one of the important causes of drug resistance in tumor cells, and it can lead to tumor drug resistance by affecting a variety of cellular pathways. Currently used drugs usually kill tumor cells by causing DNA damage and promoting cell apoptosis to treat cancer, while abnormal DNA methylation causes abnormal gene expression in related pathways, thereby affecting cancer drug resistance. The increased methylation level of the promoter of the hMLH1 gene, which encodes a DNA mismatch repair enzyme, leads to a decrease in gene expression, thereby resulting in cisplatin resistance in ovarian cancer cells [10]. CASP8 is a pro-apoptotic gene and a key factor in the death receptor-mediated apoptotic pathway. In various tumor cells, the promoter of the CASP8 gene is methylated, making tumor cells resistant to a variety of chemotherapeutic drugs such as doxorubicin, etoposide, and cisplatin [11].

During the process of drug action, drugs undergo absorption, transport, metabolism, and other processes. DNA methylation causes abnormal drug efflux and metabolism by affecting the expression of proteins that play a key role in this process, thereby leading to drug resistance. MDR1 is an important ATP transport protein. Clinical data show that the expression of MDR1 in bladder cancer patients after chemotherapy is 3.5-5.7 times higher than that before chemotherapy and eighty-nine

percent of recurrent patients have high MDR1 expression, and the level of expression of MDR1 is significantly inversely correlated with the methylation level of its gene promoter [12]. In addition, CYP3A is a drug-metabolizing enzyme, when the expression of CYP3A increases due to changes in the methylation level of its gene, it can reduce the pharmacological activity of paclitaxel, making colorectal cancer cells tolerant to paclitaxel [13]. Wang's team found that the decreased methylation level of the OCT4 promoter in drug-resistant liver cancer tissues led to an increase in the transcriptional level of OCT4, and overexpressing OCT4 in sensitive cells or interfering with OCT4 expression in drug-resistant cells can correspondingly enhance or reduce the drug resistance of tumor cells to chemotherapeutic drugs [14]. As a stemness factor, OCT4 indicates that DNA methylation can also cause cancer drug resistance by affecting cancer stem cells.

Abnormal genome-wide methylation levels in tumor cells may also be one of the causes of drug resistance. The specific mechanism leading to changes in genome-wide methylation levels is still unclear. Some studies suggest that drug-induced replication fork stalling prolongs the interaction time between DNMTs and newly synthesized DNA, while other studies indicate that abnormal expression of DNMTs affects genome-wide methylation levels. Both a decrease and an increase in genome-wide DNA methylation levels may affect the drug resistance of tumor cells. Kastl's team used docetaxel to induce MDA-MB-231 and MCF7 cells to obtain two docetaxel-resistant cell lines, and the detection showed that the genome-wide methylation level increased in MCF7-resistant cells, while it slightly decreased in MDA-MB-231-resistant cells [15]. LINE-1 is an autonomous retrotransposon that can encode ORF2 protein with endonuclease activity, which can cause DNA double-strand breaks and genomic instability [16]. In most cases, the LINE-1 promoter is silenced due to high methylation, but under certain special circumstances, the LINE-1 promoter can be demethylated and activated. Currently, there is no accurate answer to how abnormal genome-wide methylation leads to drug resistance, but many pieces of evidence suggest that abnormal methylation levels can cause genomic instability, which in turn leads to the selection or induction of mutations that make tumor cells drug-resistant.

(2) Histone Modification

Similar to DNA methylation, histone modification involves the catalysis of specific enzymes to carry out different chemical modifications on histones, thereby affecting the up-regulation or down-regulation of gene expression. Therefore, histone modification also mainly causes tumor cells to develop drug resistance by affecting the expression levels of certain key proteins. A decrease in acetylation levels promotes the development of drug resistance. For instance, administering the HDAC inhibitor PCI-24781 results in elevated acetylation levels, this process diminishes the precision of double-strand break (DSB) repair in WiDr colorectal cancer cells and SiHa cervical cancer, thereby decreasing their radioresistance [17]. In addition, histone ubiquitination also affects tumor drug resistance through the DNA damage repair pathway. For example, USP7 promotes chemotherapy resistance in cervical cancer by preserving the stability of Chk1 protein and diminishing the DNA damage response [18].

Many studies have shown that histone methylation plays a crucial role in regulating the expression of PD-L1. LSD1 regulates the expression of PD-L1. In colorectal cancer (CRC) cells, LSD1 expression exerts an impairing effect on the TCF1+PD-1 precursor subset of CD8+ T cells within the tumor microenvironment, in turn elevating the body’s resistance to PD-1-based therapy [19]. It has been reported that histone lactylation is also associated with immunotherapy resistance. In a recent study, H3K9la was found to be positively correlated with the expression of IL-11 in patients and unfavorable immunotherapeutic responses [20].

Other studies have shown that histone modification regulates the migration, invasion, and apoptosis of cancer cells by regulating the transcriptional activity of oncogenes, thereby affecting resistance to protein kinase inhibitors [21]. For instance, HDAC11 strengthens the self-renewal potential of lung adenocarcinoma stem cells and facilitates resistance to EGFR inhibitors through enhancing Sox2

expression [22]. In addition, the combination of EGFR inhibitors and HDAC inhibitors displays promise as putative pharmaceutical interventions for cancer, which can promote cell apoptosis by activating caspases 3/7 [23].

(3) Other Epigenetic Mechanisms

Chromatin remodeling complexes are key modulators of chromatin accessibility and gene expression. Mutations in the SWI/SNF complex are found in around 20% of cancer cases and have a significant impact on treatment responses [24]. Perturbations of the BAF complex have been shown by recent research to profoundly modulate responses to targeted therapeutic strategies, and this effect is especially notable when considering sensitivity to PARP inhibitors [25]. Significantly, alterations in chromatin accessibility usually occur before the emergence of drug resistance, which indicates that they are incipient markers of therapeutic failure [26].

ncRNAs also cause drug resistance by affecting a variety of mechanisms. Dysregulation of MicroRNA, especially overexpression of miR-21, is observed in 75% of drug-resistant instances and has a substantial impact on treatment results [27]. Depletion of members of the miR-200 drives the epithelial to mesenchymal transition and the progression of drug resistance that follows, which constitutes a critical mechanism underlying adaptive resistance [28]. In addition, specific microRNA profiles have been shown to be useful in forecasting the effectiveness of treatment, which indicates their possible ability as biomarkers [29].

Epigenetic mechanisms such as histone modification, DNA methylation, and ncRNAs form a complex network that coordinates gene expression patterns, thereby affecting cellular processes and leading to the occurrence and development of cancer. These epigenetic marks interact with each other, which may lead to the activation of oncogenes or the inhibition of tumor suppressor genes, thereby regulating the behavior of cancer cells and interfering with the prognostic response of cancer treatment.

4. EPIGENETIC DRUGS AND CANCER TREATMENT

In the above content, we have summarized in detail the effects of various epigenetic regulations on the development of tumor drug resistance. Targeting important epigenetic factors is an innovative method for the treatment of malignant tumors. The current application of epigenetic drugs in cancer treatment mainly focuses on inhibiting abnormal DNA methylation, histone methylation, and histone acetylation [30]. Up to now, the FDA has approved a number of drugs directed at epigenetic mechanisms of specificity, these include DNA methylation inhibitors like decitabine and 5-azacytidine, HDAC inhibitors like chidamide, vorinostat, and romidepsin, along with the EZH2 inhibitor tazemetostat [31].

Moreover, the synergy of epigenetic therapy with other treatment modalities may serve as a novel approach for cancer treatment and ensuring prognostic effects. Currently, some studies have suggested the potential of combined therapy with ErbB inhibitors and HDAC inhibitors for the treatment of breast cancer or non-small cell lung cancer, but no significant reversal of drug resistance has been observed [6]. Some other studies have tested the synergy of hormone therapy with epigenetic drugs. Results from an ongoing phase II clinical trial have shown that the combined use of HDAC inhibitors and antiestrogens/aromatase inhibitors exhibits certain therapeutic effect and a reduction in drug resistance. Among the participants, 43 breast cancer patients received vorinostat combined with tamoxifen treatment: 8 patients had a lasting objective response, and 9 patients experienced stable disease. These results are undoubtedly encouraging [32].

5. CONCLUSION

In recent years, based on the combination of multiple disciplines such as genetics, biochemistry, molecular biology, and cell biology, as well as the application of new technologies, we have fully explored the epigenetic mechanisms' involvement in cancer and cancer drug resistance. These findings have enabled us to understand the mechanism of cancer drug resistance and provided a basic principle for the innovation of drugs targeting epigenetic factors.

Currently, some epigenetic drugs have been used, and there are many drugs in the clinical trial stage. The use of epigenetic drugs has also shifted from single-drug use to combination with other drugs for treatment. In some types of cancer, the use of epigenetic drugs has shown the potential to reverse drug resistance. However, we must also admit that even if some drugs are effective, drug resistance may still develop again. This is the result of the mutual regulation of the complex cancer epigenetic network. Of course, we should always believe that through continuous exploration to understand the mechanism of cancer drug resistance in detail and promote drug development, the hope of curing cancer will continue to improve.

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