Epigenetic Modifiers: Key Players in Overcoming Cancer Resistance

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***Abstract*: Cancer resistance remains a major challenge, reducing the effectiveness of chemotherapy, immunotherapy, and targeted therapies. Epigenetic modifications, like histone modifications and DNA methylation, regulate gene expression and contribute to tumor progression and drug resistance. Key epigenetic modifiers, including DNMTs, HDACs, KDMs, and PRMTs, have emerged as potential therapeutic targets. Epigenetic inhibitors, alone or in combination with conventional therapies, have shown promising outcomes in overcoming resistance and improving treatment outcomes. This review explores the role of epigenetic modifications in cancer resistance and highlights recent advancements in epigenetic-targeted therapies.**

***Index Terms*: Epigenetic Modifiers, Cancer Resistance, DNA Methylation, Histone Modifications, Tumor Microenvironment, Epigenetic Therapy**

I. INTRODUCTION

Cancer is a global health burden that results in the death of % of people every year. Cancer resistance is one of the factors that reduces the effects of various treatments such as chemotherapy, targeted therapies, and immunotherapies which lowers the chances of a patient's survival. Epigenetic modifications, such as DNA methylation and histone modifications help in the development and regulation of cancer resistance Alterations in gene expression by epigenetic modifiers result not only in the growth and survival of cancer cells but also help in the development of resistance against therapeutic agents used during the treatments. Recent studies on mechanisms have shown various approaches to address the issues. This review explores the role of epigenetic modifiers in overcoming cancer resistance, focusing on specific mechanisms and pathways involved.

II. MECHANISMS OF EPIGENETIC REGULATION IN CANCER RESISTANCE

Cancer resistance can also develop due to various factors which includes genetic mutations, epigenetic alterations, and tumor microenvironment interactions Although epigenetic modifications, such as DNA methylation and histone modifications, are reversible but play an important role in the regulation of gene expression. These changes can result in tumor suppressor gene silencing, oncogene activation, and cancer stem cell (CSC) survival and metastasis promotion [1] [2].

A. DNA Methylation

DNA methylation is a well-studied epigenetic DNA methylation is the addition of methyl groups to cytosine residues in DNA, which results in gene silencing. It is one of the widely researched epigenetic modifications The hypermethylation of tumor suppressor genes and hypomethylation of oncogenes contribute to tumorigenesis as well as resistance to therapies [2] [3]. Aberrant patterns of DNA methylation, especially hypermethylation of tumor suppressor genes, lead to chemoresistance. For example, methylation of the promoter region of genes involved in DNA damage repair (such as MGMT and BRCA1) is associated with the development of resistance to therapies, including alkylating agents and platinum-based chemotherapies. This methylation can inhibit the g capacity of gene to repair DNA damage from these treatments, enabling cancer cells to survive and resist the therapies. [4] [5]

B. Histone modification

Acetylation, methylation, and ubiquitination are forms of histone alteration that modify chromatin structure affecting gene expression. For example, histone acetylation (HAT) causes chromosome to loosen and genes to be expressed, whereas histone deacetylation (HDAC) leads to chromosome tightening and gene expression suppression [6] [7]. Two of the major post-translational changes which affect chromatin and gene expression are acetylation and methylation of lysine residues. Several specific histone deacetylases (HDACs) and K-lysine specific demethylases (KDMs) have been shown to induce

tolerance to certain drugs by shifting the metabolic profile towards the expression of cancer stem cells and initiating epithelial-mesenchymal transition (EMT) [8] [9].Cancer stem cells (CSCs) are a group of undifferentiated cancer cells which can proliferate endlessly in culture by undergoing differentiation into mixed cell types and are implicated in tumorigenesis, progression, and resistance to therapies. They are epigenetically regulated by means of histone and DNA methylation that alter the CSC mark proteins expression together with tumor plasticity in the ability to survive and metastasize [1] [10]. The process called epithelial to mesenchymal transition (EMT) describes the transformation of epithelial cells to mesenchymal phenotypes.

C. Noncoding RNA

MicroRNAs (miRNA) and long noncoding RNAs (lncRNA) modulate gene expression after transcription, thereby affecting drug resistance. For instance, miRNAs can target DDR genes, which impacts chemotherapy response [10] [11].

D. Chromatin Remodelling

Remodelling of chromatin involves changes in the structure of chromatin that affect gene expression and accessibility. Disruptions in the chromatin remodelling complexes, e.g., mutations or alteration of the expression of chromatin-modifying enzymes, are typical for cancer and facilitate malignant transformation [12]

III. SPECIFIC EPIGENETIC MODIFIERS AND THEIR ROLES IN CANCER-RESISTANCE

Several epigenetic modifiers have been identified as major players in cancer resistance. These include histone deacetylase (HDACs), DNA methyltransferases (DNMTs), histone demethylases (KDMs), and protein arginine methyltransferases (PRMTs). Targeted modulation of these modifiers can effectively overcome cancer resistance.

A.DNA methyltransferases (DNMTS)

DNMTs are enzymes that ensure the preservation of DNA methylation patterns. DNMT overexpression occurs in cancer, leading to hypermethylation of tumor suppressor genes and silencing of their expression. DNMT inhibitors like 5-azacytidine and decitabine, have been used to reverse DNA methylation and restore the expression of tumor suppressor genes, making cancer cells sensitive to therapy [2] [7].

B. Histone deacetylase (HDACs)

HDACs decrease the acetylation on a histone by removing acetyl groups, which allows for the condensation of chromatin and gene silencing. During cancer stages, HDACs are characteristically overexpressed and aid in the silencing of tumor suppressor genes. HDACs have potent suppressive impacts on tumor activation, enabling the development of hyperacetylated quasi-methylated histone regions along with tumorigenic HDAC inhibitors (HDACis). In breast cancer, the HDAC inhibitor entinostat induces T cell-inflamed bladder cancer microenvironment, enhancing the activity of anti-PD-1 treatment [13].

C. Histone Demethylases (KDMS)

KDMs are histone demethylases that removes methyl group from histones and modulate gene expression. In cancer, KDM4 and KDM5 KDMs increase drug resistance by changing the expression survival patterns of the cancer cells. JIB-04 KDM inhibitors cause DNA damage and immunogenic cell death with the release of\ Antitumor-reactive cells and dominant tumor-based innate immunity and lead to enhanced immunogenic cell death [14] [7].

IV. PROTEIN ARGININE METHYLTRANSFERASES (PRMTS)

Protein arginine methyltransferases (PRMTs) PRMTS are a subclass of arginine methyltransferases catalyzing the methylation of opened histones PRMT 1 and, PRMT 5 In cancer they increase the drug resistance by altering the drug efflux transporters and autophagy and DNA damage repair. PRMT 1 and 5 in Zhu et al 2023 showed that PRMT inhibitors helped developing sensitivity against the anticancer drugs used in chemotherapy, targeted therapy, and immunotherapy [15].

V. THERAPEUTIC STRATEGIES TARGETING EPIGENETIC MODIFIERS

Several epigenetic drugs have been developed to reverse resistance mechanisms and restore therapeutic sensitivity in cancer cells.

A. DNA Methyltransferase Inhibitors

5-Aza 2′-deoxycytidine (5-aza-D) is an example of a compound that acts as a DNA methyltransferase inhibitor by intervening through two pathways of DNA methylation reversal to restore lost empirical

sensitivity. For example, patients of bladder cancer become resistant to cisplatin, which can be reversed by treatment with 5-aza-D because of its ability to demethylate the HOXA9 promoter [16] [5].

B. Histone Deacetylase (HDAC) Inhibitors

Romidepsin and vorinostat are known deacetylase (HDAC) inhibitors. They act on the acetylated form of histones and thus cause chromatin remodelling through the activation of tumor suppressor genes. It is preferable to use these agents in combination with chemotherapy and immunotherapy [11] [16]

C. Histone Methyltransferase and Demethylase Inhibitors

EZH2, a histone methyltransferase, and LSD1, a lysine demethylase, are known Histone Methyltransferase and Demethylase Inhibitors and are researched to alleviate epigenetic silencing of the DNA damage response (DDR) genes to render cancer cells more responsive to treatment [8] [11].

D. Histone Deacetylase (HDAC) Inhibitors

HDAC inhibitors, such as vorinostat and romidepsin, modulate histone acetylation, leading to chromatin remodeling and reactivation of tumor suppressor genes. These drugs have shown promising results in combination with chemotherapy and immunotherapy [11] [17]

E. Non-Coding RNA Therapies

miRNA mimics and lncRNA inhibitors have been investigated to suppress epigenetic regulators in targeting to restore chemosensitivity [11] [18].

VI. COMBINATION THERAPIES INVOLVING EPIGENETIC MODIFIERS

Although epigenetic modifiers as monotherapies have been promising, their effectiveness is limited when used alone. The simultaneous addition of combination drugs, along with epigenetic modifiers, along with traditional anticancer therapy, has been found to exhibit greater treatment effects and can counteract resistance

A. Epigenetic modifiers and chemotherapy

Epigenetic modifiers have also been used in combination with chemotherapy to increase the sensitivity of cancer cells to chemotherapeutic agents. For instance, HDAC inhibitors have been combined with chemotherapy and were said to re-express the expression of tumor suppressor genes and make chemotherapeutic drugs more effective in several types of cancer, including prostate cancer and glioblastoma [19] [20].

B. Epigenetic modifiers and immunotherapy

Epigenetic modifiers have also been combined with immunotherapy to enhance the efficacy of immune checkpoint inhibitors. For example, HDAC inhibitors combined with anti-PD-1 therapy promote the T cell-inflamed tumor microenvironment and increase antitumor activity in bladder cancer [13]. Similarly, KDM inhibitors trigger tumor-intrinsic innate immunity and combine with immunotherapy to enhance their antitumor effects [14].

C. Epigenetic modifiers and targeted therapies:

Epigenetic modifiers are used along with targeted therapies to reverse resistance. For example, when used in combination with targeted therapies, DNMT inhibitors reactivate tumor suppressor gene expression and increase therapeutic activity in breast cancer and melanoma [10]. In targeted therapy resistance, epigenetic inhibitors reverse resistance by manipulating oncogenic pathways. For example, HDAC inhibitors have been used in combination with EGFR inhibitors to reverse resistance to lung cancer [10] [21].

VII. CHALLENGES

Despite the promise of epigenetic treatments, some challenges persist:

A. Suppressed Solid Tumor Efficacy

The solid tumor efficacy of epigenetic therapy has been variable and has created a need for additional studies with combination regimens and patient selection strategies [22] [18].

B. Toxicity and Resistance

Therapy with epigenetic drugs typically has side effects, and cancer cells can also develop resistance to therapy through adaptive mechanisms [17] [23].

Biomarker Identification

Identification of biomarkers for predicting patient outcomes after epigenetic therapy is crucial for the personalization of therapy regimens. Methylation of DDR gene promoters, for example, can be used as potential biomarkers for patient stratification [4] [13]. The relationship between metabolic and epigenetic

changes in neoplastic cells must be research further to develop new therapeutic interventions [25].

VIII. CLINICAL ADVANCEMENTS

Although the clinical use of epigenetic therapies has been very promising, it remains quite difficult. First of all, the clinic needs new epigenetic drugs that are more potent and target specific. Furthermore, developing predictive biomarkers for the stratification of patients based on epigenetic changes will help in the identification of those most likely to benefit from these therapies [2] [7]. There are various clinical trials underway that seek to evaluate the efficacy of epigenetic modifiers alongside other anticancer therapies. For instance, there seems to be some excitement in integrating HDAC inhibitors with anti-PD-1 therapy in patients with solid tumors because of the increased anti-tumor activity and improved results that have been noted [13] [24].

IX. FUTURE DIRECTIONS

Additional research will need to analyze the link between epigenetic modifications and resistance to treatment, while also identifying novel agents that possess higher specificity and efficacy. Moreover, the development of predictive biomarkers, as well as reasonably crafted multi-targeted strategies, will be pivotal in the comprehensive application of epigenetic modulation in cancer control [7] [24].

X. CONCLUSION

The problem of drug resistance in cancer that is caused by epigenetic modification can be dealt with by focusing mechanistic and pathway-based approaches that drive tumor growth and drug resistance. The use of a conventional (first line) anticancer treatment together with an epigenetic modifier is more effective as it improves the therapeutic effect and surmounts resistance. More research is required to elucidate the complex dynamics of epigenetic modification and drug resistance from which better cancer treatment solutions can be derived. [1]

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