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# Epigenetic Targets in Cancer Therapy: A Pharmacological Review of Histone Modifiers and DNA Methylation Inhibitors

*Author(s): Dakush Mahajan[1], Firoz Khan[2], Shafkat Hussain Malik[3*] , Ruhit Ashraf[4] ,Mudasir Majeed [5]*

[1,] B. Pharmacy (Student), School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab

[2,,3] Assistant Professor, School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab

[4]Associate Professor, S. Lal Singh Memorial College of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab

[5,,] B. Pharmacy (Student), School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab.

Corresponding Email: shafkat2016@gmail.com.

**Abstract**

Cancer is a multifactorial and complex disease, and it is hereditary as well as epigenomically modified. A permanent change in the code of the DNA on the other, is genetic mutation, but a control of gene expression, without altering the genetic code upon which it is based, is called an epigenetic modification. Chromatin structure and gene transcription regulation modification of DNA methylation and histone play a significant role in preserving normal cell identity and cell functions. The epigenetic changes are not permanent and, in contrast to the genetic mutations that are generally irreversible, they can be reversible, and there is only one possibility of a curative intervention. That has resulted in the development of epigenetic drugs that regulate the activity of important enzymes that write, read or erase epigenetic marks. Histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), histone demethylases and DNA methyltransferases (DNMTs). FDA approved epigenetic therapies (mostly against hematologic malignancies, although many more have been in preclinical and clinical trials against hematologic and solid tumors) already exist and nowadays there are many more in preclinical and clinical trials against hematologic and solid tumors. It also talks about clinical possibility of approved epigenetic drugs approved so far, new therapeutic transactions and combination. And, lastly, we consider general problems like resistance to drugs, off-target effects and predictive biomarkers and guidelines on how to improve the accuracy and efficacy of epigenetic therapy in cancer.

**Keywords:** Cancer, Epigenetics, Histone Modifiers, DNA Methylation, Histone Deacetylase Inhibitors

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## 1. Introduction

The etiology of cancer and its subsequent progression is a complex interaction of genetic and epigenetic changes which interfere with the highly delicate processes that govern cell proliferation, differentiation, and programmed cell death (apoptosis) [1]. Whereas genetic mutations are the irreversible changes in the sequence of DNA, the epigenetic alterations are reversible, heritable changes in gene expression that do not require any change in the sequence of nucleotides [2]. Such changes in the epigenome play a crucial role in defining chromatin structure and accessibility of particular genes to the transcriptional apparatus, ultimately shaping whether certain genes are activated or repressed [3]. DNA methylation and histone modifications are some of the best-characterized mechanisms of epigenetics. DNA methylation generally entails the attachment of methyl groups on cytosine bases on CpG islands, which often leads to the inactivation of the expression of specific genes [4]. Nonetheless, histone modifications refer to post-translational modification of the histone proteins to which DNA is packed. These are acetylation, methylation, phosphorylation and ubiquitination [5]. Taken together, these changes contribute to either relaxation (transcriptionally active) of chromatin (euchromatin) or its condensed (transcriptionally silent) state (heterochromatin). These epigenetic processes are not regulated in cancer. Promoters of tumor suppressor genes may be hypermethylated, and oncogenes may be hyperactivated [6]. These epigenetic imbalances are no longer considered peripheral factors in tumor pathogenesis, they are now considered core elements in tumor initiation, progression, metastasis, and resistance to current therapies against tumors such as chemotherapy, radiation, and even specific therapies [7]. Significantly, epigenetic alterations are reversible and dynamic, unlike fixed genetic mutations and are, therefore, especially appealing as targets of therapy. Significant progress has been achieved over the last several decades in the understanding of the molecular basis of epigenetic regulation and in the development of agents that may be manipulated to alter these processes [8]. It is known that there are several classes of enzymes that control epigenetic states. These are histone acetyltransferases (HATs), which can add acetyl groups to histones to activate the gene, and histone deacetylases (HDACs), which can remove them and cause chromatin to be compressed, silencing the gene [9]. In a similar fashion, histone methyltransferases (HMTs) and histone demethylases control the histone methylation state which may activate or suppress gene expression depending on the residues that are modified. Simultaneously, DNA methyltransferases (DNMTs) catalyze the incorporation of methyl groups into an existing piece of DNA, which in many cases leads to transcriptional silencing [2]. Small molecule drugs that inhibit these epigenetic regulators have already been granted clinical approval,

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including DNMT inhibitors (e.g., azacitidine and decitabine), and HDAC inhibitors (e.g., vorinostat and romidepsin) [10]. Furthermore, there is an increasing amount of preclinical and clinical evidence regarding the usefulness of epigenetic therapy in solid tumors, as a monotherapy or in combination with additional therapeutic approaches [11]. Epigenetic drugs could be used in combination with chemotherapy, targeted therapy, or immunotherapy to overcome the resistance mechanism and enhance the efficacy of treatments. Such combinations are being tested in current clinical trials in many different kinds of tumors [12]. The review also gives a detailed analysis of the main epigenetic regulators, which include histone modifiers and DNA methylation inhibitors, how they work, their clinical significance, and how they may be used as part of complete cancer therapies [13]. Continued efforts toward identifying biomarkers, patient stratification, and next-generation epigenetic drugs are necessary to maximize the therapeutic potential of epigenetic regulation to treat cancer [14].

## 2. Epigenetic Mechanisms in Cancer

The epigenetic regulation has been defined as a series of inheritable, though reversible, biochemical changes, which regulate the expression level of the genes, but does not modify the sequence of DNA [15]. This architecture entails mainly covalent chemical alterations of DNA and histone proteins: the major components of chromatin, the highly compact structure assembly, which contains the genetic material of eukaryotic cells located in their nucleus. These changes include DNA methylation, and a host of post-translational histone tail modifications, among them acetylation, methylation, phosphorylation, and ubiquitination, which have acquired sufficient functional roles [16]. Epigenetic marks adjust the chromatin architecture by varying the degree to which DNA is tightly or loosely coiled around the inner cores of histone proteins and, consequently, they regulate the accessibility of genes to transcriptional factors and other transcriptional machineries [17]. As such, euchromatic and heterochromatic states enhance and suppress transcriptional and gene expression respectively. Epigenetic regulation plays a key role in many cellular events, including differentiation, development, X -chromosome inactivation, genomic imprinting and environmental sensitivity [18]. It is worth noting that such a regulatory system is dynamic in nature - capable of responding to both intracellular and extracellular signals - and reversible, enabling the gene expression to be turned down or up, according to the time of day. Therefore, epigenetics is an important regulatory system that ensures the identity and integrity of cells. [19]

### 2.1 DNA Methylation

The term epigenetic regulation describes a very wide variety of heritable and reversible changes to both DNA and histone proteins that affect the expression of genes but do not affect the underlying sequence of DNA. These changes are made in chromatin, the combination of DNA and histone proteins which package and organize genetic material in the nucleus.

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Examples of important epigenetic processes are DNA methylation, in which cytosine residues in DNA are methylated, generally silencing gene expression, and other forms of post-translational modifications (PTM) of histone tails [20]. These PTMs are acetylation, methylation, phosphorylation, and ubiquitination, all of which activate or repress transcription depending on the site and form of the particular modification. These chemical modifications affect the availability of DNA to transcriptional machineries by modifying the physical structure and level of compaction of chromatin [21]. As an illustration, it is known that the acetylation of histones tends to ease the structure of the chromatin, increasing the availability of genes to transcription, while the DNA methylation tends to compact and silence genes [22]. Epigenetic control is essential in the establishment of cell identity and cell function, and in directing cell differentiation in development and in enabling cell adaptive response to environmental signals [23]. Notably, these changes are dynamic and reversible and enable adaptation of gene regulation throughout the life of an organism and are involved in a wide range of biological processes and pathogens, such as cancer and aging [24].

### 2.2 Histone Modifications

Histone proteins can undergo post-translational modifications that include acetylation, methylation, phosphorylation, ubiquitination and sumoylation. These chemical alterations alter the structure of chromatin, and as a result, affect the expression of genes [25]. Two important categories of histone modifiers are: Physical characteristics: 1) is the protein that the histone proteins interact with to form a complex, 2) is a deacetylase protein, which is present in nearly all cells, 3) activates or suppresses certain genes [26]. HATs were found to accept acetyl groups onto the lysine residues, resulting in a relaxed chromatin state and transcriptional activation, and to donate acetyl groups by HDACs, resulting in chromatin condensation and gene repression **(Figure 1)** [27]. Histone Methyltransferases (HMTs): HZGA1- NPN, HZGA2- NPN, HZGA3- NPN, HZGA4- NPN, HZGA5- NPN, HZGA6- NPN, HZGA7- NPN, HZGA8- NPN, HZGA9- NPN; HZGA10- NPN; HZGA11- NPN; HZGA12- NPN; HZGA13- NPN; HZGA14- N; The role of changes in the functions of these enzymes in the pathogenesis of cancer is very important.

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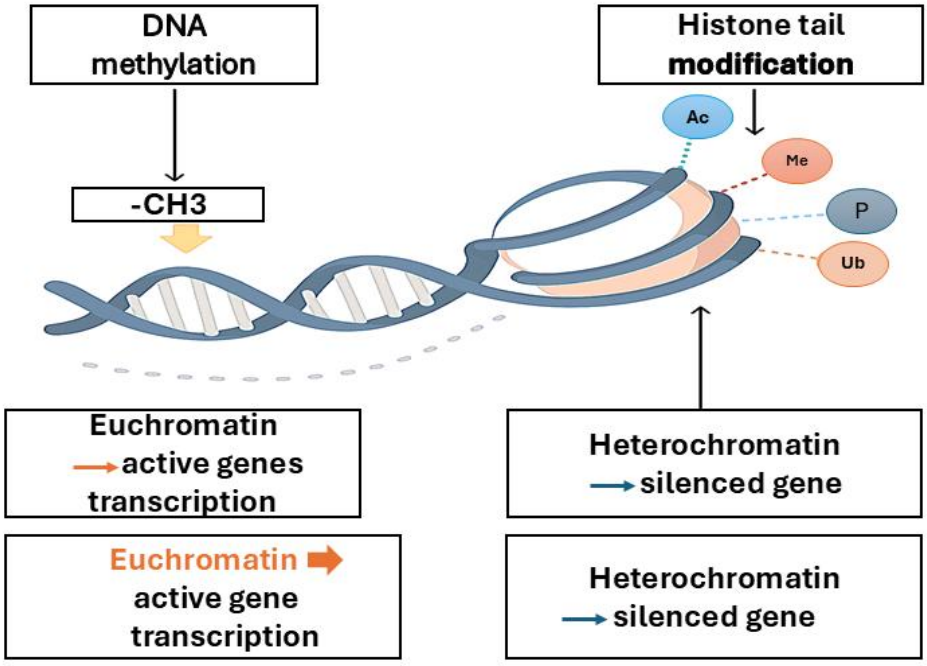


**Figure 1:** Epigenetic Regulation in Cancer

## 3. Histone Modifiers as Therapeutic Targets

### 3.1 Histone Acetyltransferases (HATs)

One such group of enzymes is historically significant in the regulation of the epigenome and are known as histone acetyltransferases (HATs) which catalyze the acetyl group transfer to the tail of histone proteins on specific lysine residues [28]. This acetylation is a neutralization of the positive charge of the lysines decreasing the histone interaction with the negatively charged DNA. Subsequently, the chromatin structure is more relaxed or open and this allows the binding of the transcriptional machinery leading to an increase in the expression of genes [29]. Nonetheless, faulty regulation of the activity of HAT may significantly lead to cancer. Increased HAT activity-abnormally- could cause overexpression of oncogenes, whereas depressed activity could cause the silencing of tumor suppressor genes. The two mechanisms interfere with the usual cell functions and foster tumorigenesis [30]. Even though HATs have been identified as significant agents in cancer, the inability to produce HAT inhibitors as drugs is in its nascent phase, with the major concerns being specificity, low bioavailability, and unwanted off-target effects [31].

### 3.2 Histone Deacetylases (HDACs)

The histone deacetylases (HDACs) are enzymes that cause the loss of acetyl groups in the lysine residues of histone tails. This removes the negative charge on the histones that enhances

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their affinity towards the negative DNA to condense into chromatin [32]. To this extent, the chromatin becomes less accessible to transcriptional machinery which causes reduction of gene expression. This process plays an important role in silencing of tumor suppressor genes and other controlling genes related to cell cycle regulation, differentiation and apoptosis [33]. Overexpression or dysregulation of HDACs is a repeated observation in most categories of malignancy such as breast, prostate, lung and hematological cancers. It is commonly assumed that this dysregulation is associated with the heightening level of aggressiveness, invasiveness and metastasis of tumours and a poor clinical outcome [34]. Due to their strong association with the development of cancer, HDACs have been a viable therapeutic intervention target. A number of HDAC inhibitors (HDACi) have been discovered and some of them have been granted FDA approval to treat specific cancers, particularly hematologic malignancies. Current studies are attempting to extrapolate their use to solid tumours and to improve their specificity, effectiveness and safety profile [35].

### 3.2.1 HDAC Inhibitors (HDAC)

Histone deacetylase (HDAC) inhibitors are a class of anticancer medications with the capacity to restore physiological histone acetylation and consequently open chromatin structure with the subsequent reactivation of silenced genes [36]. These reactivated genes tend to encode important cell processes, among them cell cycle progression, differentiation, and apoptosis. HDAC inhibitors are able to reverse the gene silencing frequently found in cancer cells, alter cell behavior to a more differentiated state, and encourage programmed cell death by causing cell cycle arrest [37]. Multiple HDAC inhibitors have been FDA approved for the treatment of hematologic cancers such as T-cell lymphomas and multiple myeloma (vorinostat and romidepsin, respectively), and research is underway with solid tumors [38]. Histone deacetylase inhibitors (HDAC) may not only suppress the work of histone deacetylase but also may have an anticancer effect of increasing the acetylation of histone and non-histone proteins [43]. This augmented acetylation modifies chromatin structure to permit simpler access, allowing silenced genes (including tumor suppressor genes) to be re-activated. Furthermore, non-histone acetylation also regulates several cell functions such as DNA repair, cell proliferation and death [44]. Collectively, HDAC inhibitors disrupt cell survival in cancer cells, leading to growth arrest, cellular differentiation and eventual programmed cell death and thus have the potential to become valuable drug targets in cancer [45].

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**Table 1: Clinically Approved HDAC Inhibitors in Cancer Therapy**

| HDAC Inhibitor | Brand Name | Approved Indication | References |
|---|---|---|---|
| Vorinostat | SAHA | Cutaneous T-cell lymphoma | [39] |
| Romidepsin | Istodax | Peripheral and cutaneous T-cell lymphomas | [40] |
| Belinostat | Beleodaq | Peripheral T-cell lymphoma | [41] |
| Panobinostat | Farydak | Multiple myeloma (in combination therapy) | [42] |

**3.2.2 Clinical Trials**: A number of clinical trials are ongoing regarding the use of histone deacetylase inhibitors (HDAC inhibitors) with other treatment modalities to treat cancer. Such combinations include conventional chemotherapy, targeted therapy, immunotherapy, and other epigenetic drugs [46]. These strategies are driven by the need to enhance the therapeutic index of monotherapies as well as to avoid resistance mechanisms that often limit the efficacy of monotherapies. HDAC inhibitors have the ability to alter gene expression, tumor microenvironment, and immune responses and can thus be combined with multi-modal treatment strategies [47]. Inhibitors of HDAC can also make cancer cells susceptible to chemotherapy or targeted therapy so that these therapies can be more effective. In the same way, during immunotherapy they can be used to improve tumor immunogenicity and enable more recognition by the immune system [48]. Such continuous experiments reflect a growing concern and interest in epigenetic modulation as a cornerstone of precision cancer treatment with the aim to increase clinical outcome and patient survival [49].

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**Table 2: Histone Modifier Inhibitors in Clinical Use and Trials**

| Inhibitor | Target | Cancer Type | Clinical Status | References |
|---|---|---|---|---|
| Vorinostat | HDAC | Cutaneous T-cell lymphoma | Approved | [50] |
| Romidepsin | HDAC | Cutaneous T-cell lymphoma | Approved | [51] |
| Panobinostat | HDAC | Multiple myeloma | Approved | [52] |
| Belinostat | HDAC | Peripheral T-cell lymphoma | Approved | [53] |
| GSK126 | EZH2 (HMT) | Non-Hodgkin lymphoma | Phase 1/2 | [54] |
| Tazemetostat | EZH2 (HMT) | Epithelioid sarcoma, lymphoma | Approved | [55] |

Table 2: Histone Modifier Inhibitors in Clinical Use and Trials

### 3.3 Histone Methyltransferases (HMTs) and Demethylases (HDMs)

Aberrant methylation of histones is a well-recognized hallmark of a wide variety of cancers, and is important not only for silencing tumor suppressor genes but also for altering normal gene expression programs [56]. This epigenetic modification plays an important role in the development of tumor initiation, progression and metastasis. Enhancer of Zeste Homolog 2 (EZH2), which is the catalytic unit of Polycomb Repressive Complex 2 (PRC2) and catalyses the tri-methylation of histone H3 on lysine 27 (H3K27me3) to compact the chromatin and repress genes, is one of the major factors in this process [57]. EZH2 is overexpressed and/or mutated in a wide range of malignancies, including solid tumours and lymphomas, functioning as an oncogene. Targeting EZH2 has proven to be fruitful with the recent approval of Tazemetostat as the first EZH2 inhibitor in the clinic [58]. In addition to EZH2, histone-modifying enzymes including histone methyltransferases (HMTs) DOT1L and G9a as well as histone demethylases (HDMs) like LSD1 and JMJD3 are being considered as therapeutic targets. Their inhibitors are in different stages of development, which open new possibilities for treatment of cancer, which is an epigenetic disease [59].

## 4. DNA Methylation and DNA Methyltransferase Inhibitors

### 4.1 DNA Methyltransferases (DNMTs)

DNA methyltransferases (DNMTs) are key enzymes which mediate methylation of cytosine bases 5 position in DNA, primarily, at CpG dinucleotides. It is a simple epigenetic event known as DNA methylation, it is involved in the control of gene expression, chromatin stabilization, and maintenance of the genome [60]. DNMTs play a role in cellular identity, differentiation, and development by changing the DNA without changing the underlying sequence. DNMTs can be of a number of different types, DNMT1 preserving existing

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methylation patterns as DNA replicates, and DNMT3A and DNMT3B laying down new methylation signals during embryonic development or in response to external signals [61]. The essential role of DNMT is to support normal cell processes and its dysregulation may result in the abnormal silencing or activation of genes. These types of epigenetic changes are often implicated in a large variety of diseases, especially cancer, in which abnormal DNMT activity has been linked to tumor progression, metastasis, and resistance to therapy [62].

#### 4.1.1 There are three main types of DNMTs:

Three main classes of DNA methyltransferases (DNMTs) have been identified, each with distinct and complementary roles in DNA methylation pattern establishment and maintenance, which are essential to normal cellular operation and development. DNMT1 is referred to as the maintenance methyltransferase. Its key role is to identify hemimethylated DNA as it replicates, and correctly recapitulate the pattern of methylation on the existing strands into the newly synthesized daughter strand [63]. This allows the epigenetic information to be stored correctly during cell division preserving cellular identity and cellular functionality. DNMT3A and DNMT3B, in their turn, can be defined as de novo methyltransferases. The enzymes are most active in embryonic development and these enzymes play a role in creating new methylation marks on previously unmethylated DNA [64]. They also react to environmental and cellular cues, and they can be dynamically regulated to change their expression in response to environmental changes. All three DNMTs play a critical role in normal growth and development [65]. Nonetheless, overexpression, mutation, or dysfunction of DNMT expression or activity has been strictly associated with multiple diseases. Specifically, abnormal DNA methylation is traditionally linked with cancer, which causes silencing of tumor suppressor genes, genomic instability, and increased tumor progression [66].

### 4.2 DNMT Inhibitors

Clinical use of two large nucleoside analog DNA methyltransferase (DNMT) inhibitors has been approved, particularly against haematological cancers, including myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML). These hypomethylating agents include: 5-Azacytidine (Vidaza) [61], Decitabine (Dacogen) [67]. The two drugs are structurally similar to cytidine and act by being incorporated into nucleic acids-DNA and in the case of 5-azacytidine also into RNA-during cell replication or transcription. After they are integrated into DNA, they covalently bond with the DNMT enzymes, thereby trapping and inactivating them. This causes functional DNMTs to be depleted and decreases the total amount of DNA methylation in the genome [68]. Since they are hypomethylating agents, their most important pharmacological effect is to revert the aberrant DNA methylation signatures in cancerous cells. Reactivation of silenced tumor suppressor genes and other regulatory genes regulating cell growth and apoptosis are possible by this hypomethylation [69]. These drugs have

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the ability to slow down the progression of the disease and treat patients by restoring a normal gene expression. Although effective, these agents usually are applied in cycles and must be monitored closely, because they may act on normal cells as well. As a result of the continuous studies the effectiveness of these medications is being enhanced, and the side effects are reduced [70].

### 4.2.2 Mechanism of Action

Incorporation 5-Azacytidine is integrated into both the RNA and the DNA during replication and transcription Decitabine is made into DNA specifically [71]. DNMT Trapping when inserted into DNA these analogs form covalent bonds with DNMT enzymes which are irreversible consequently trapping them [72]. Enzyme depletion the result of such trapping is active DNMT functional depletion which stops further methylation activity [73]. Hypomethylation/Gene Reactivation the reactivation of formerly silenced tumor suppressor genes can be achieved by hypomethylation of DNA caused by epigenetic therapy (i.e. inhibitors of DNA methyltransferase (DNMT). Such genes are important in regulating cell growth, inducing apoptosis, as well as stability of the genome, hence play a key role in the anti-cancer effects of such therapy [74].

### 4.3 Clinical Applications

Applications of DNA methyltransferase (DNMT) inhibitors: This type of inhibitor is mainly used in hematologic cancers (myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) [75]. In these disorders, these agents have demonstrated considerable clinical advantages in reversing abnormal DNA hypermethylation and silenced tumor suppressor gene reactivation [76]. Although their efficacy has been clearly demonstrated in hematologic cancers, their application in solid tumors is still in its infancy because of issues like drug delivery, heterogeneity, and resistance mechanisms in tumors [77]. Nevertheless, research and clinical trials are currently in progress to evaluate their potential uses in a range of solid tumors, both as a single agent and as a combination therapy with alternative treatment options, such as immune checkpoint inhibitors and histone deacetylase (HDAC) inhibitors [78].

### 4.3 Limitations and Resistance

#### 4.3.1 Dose-limiting toxicities and off-target effects:

Nucleoside decitabine and nucleoside analogs of DNMT inhibitors such as 5-azacytidine and decitabine are linked to myelosuppression and side effects on the gastrointestinal system. Such unwanted effects usually restrict the dose and length of therapy, affecting treatment results. Also, off-target effects can cause unwanted change in gene expression in normal cells [79].

**4.3.2. Resistance through DNMT mutations or compensatory epigenetic mechanisms:** Mutations in DNMT enzymes that make them unable to bind the drug may cause cancer cells to become insensitive to DNMT inhibitors.

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Moreover, compensatory epigenetic changes, e.g. modulation of histone modification patterns or activation of other methyltransferases, may contribute to gene silencing in order to limit drug effectiveness [80].

**4.3.3. Poor pharmacokinetics for nucleoside analogs:**

The nucleoside analog DNMT inhibitors are characterized by rapid degradation and low stability in vivo resulting in inefficient drug exposure and clinical benefit. In order to address these shortcomings and enhance treatment response of non-nucleoside DNMT, newer non-nucleoside DNMT inhibitors and combination therapy are currently in trial [81].

| Inhibitor | Target | Cancer Type | Clinical Status | References |
|---|---|---|---|---|
| 5-Azacytidine | DNMT | Myelodysplastic syndrome (MDS) | Approved | [82] |
| Decitabine | DNMT | MDS, AML | Approved | [83] |
| Guadecitabine | DNMT | AML | Phase 2/3 | [84] |
| Zebularine | DNMT | Experimental | Preclinical | [85] |

Table 3: DNA Methylation Inhibitors and Clinical Applications

## 5. Combination Therapies and Emerging Strategies

### 5.1 Rationale for Combinations

Solo-agent epigenetic therapy (e.g., DNA methyltransferase (DNMT) or histone deacetylase (HDAC) inhibitor therapy) has shown significant clinical potential in some hematologic malignancies, including myelodysplastic syndromes and some leukaemia's [86]. Nonetheless, it has been ineffective in the treatment of solid tumors since it has not been successful in overcoming a couple of challenges, such as high tumor heterogeneity, the emergence of drug resistance, and inadequate drug penetration into the tumor microenvironment [87]. Combination therapies in which epigenetic drugs are used together with chemotherapy, immunotherapy, or targeted therapy are actively investigated to overcome these constraints. These integrated strategies attempt to improve the efficacy of therapy and resistance strategies in solid tumor therapy [88].

### 5.2. Overcome resistance:

DNA methyltransferase (DNMT) inhibitors or histone deacetylase (HDAC) inhibitors together with the traditional chemotherapy or targeted therapeutic drug have shown great potential in overcoming drug resistance in cancer treating

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[89]. The bulky epigenetic medications have the ability to reverse the atypical gene silencing that aids in the resistance by reactivating the tumor suppressor genes and reinstating the normal cellular pathways [90]. DNMT and HDAC inhibitors can increase the sensitivity of cancerous cells to other treatments by changing the chromatin structure and changing the pattern of gene expression. Such type of a combinational methodology assists in re-establishing drug responsiveness in previously resistant cancer cells, which increases the overall effectiveness and efficacy of cancer therapies [91].

### 5.3. Enhance antitumor immune response:

Epigenetic therapies can be used together with immunotherapies to improve the immunological capability to identify, locate and destroy cancerous cells. Epigenetic drugs (DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors have the potential to re-express immune-related genes that are commonly suppressed in cancer cells [92]. This contains genes of antigen presentation, interferon signaling and co-stimulatory pathways. Reactivating these genes causes the tumor to be easier to see by immune cells, and thus enhances the overall tumor response to immunotherapy [93].

### 5.4. Increase cancer cell sensitivity to DNA damage:

The integrity of the DNA repair pathways as well as the organization of the chromatin in the cancer cells can be disrupted by epigenetic agents including DNA methyltransferase (DNMT), histone deacetylase (HDAC) inhibitors. Such interference causes tumor cells to be more susceptible to DNA-damaging agents, such as radiation therapy and cytotoxic chemotherapy [94]. Epigenetic drugs increase the cytotoxic effects of therapy by preventing the repair process of DNA damage inflicted by these treatments in the cancer cell. This is why using epigenetic agents together with DNA-damaging therapies may lead to a substantial improvement of the overall therapeutic results and treatment effectiveness [95].

### 5.5 HDACi and DNMTi Combinations

DNA methyltransferase (DNMT) inhibitors have demonstrated considerable potential with histone deacetylase (HDAC) inhibitors in cancer therapeutics, especially in a preclinical model of both hematologic malignancies and solid tumors. DNMT inhibitors operate by decreasing DNA methylation which in most cases are central to silencing tumor suppressor genes [96]. DNMT inhibitors by depriving the methyl groups of cytosine residues facilitate a more transcriptionally active state of the genome. The HDAC inhibitors, in turn, act through the enhancement of the acetylation of the histone proteins, resulting in the appearance of a less rigid chromatin structure and the increased accessibility of the transcriptional machinery [97]. This bilateral strategy, which reduces methylation and enhances acetylation levels simultaneously, has been found to synergistically activate silenced genes which mediate vital cellular processes. DNA methyltransferase and HDAC inhibitors can be combined to lead to a more efficient re-expression of cell cycle

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regulation, apoptotic and immune response pathways genes [98]. This causes more cancer cell death, decreased tumor growth and also sensitivity to other therapies is increased. The combination has worked especially well in triggering apoptosis and abridging proliferation in other cancer models. In general, this form of therapy is a viable epigenetic direction in treating cancer but additional clinical trials are required to maximize dosage, schedule, and to reduce any adverse reactions [99].

### 5.6. Epigenetic Therapy and Immunotherapy

Epigenetic drugs, such as DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors are of significant use not only in controlling the activities of genes but also in controlling the tumor microenvironment to enhance the effectiveness of cancer immunotherapy [13]. These agents have the ability to up-regulate the expression of antigen presentation related genes, co-stimulatory molecule, and interferon signaling pathways. In particular, it has been demonstrated that DNMT and HDAC inhibitors induce the expression of tumor-associated antigens (TAAs) and the major histocompatibility complex (MHC) molecular class I and II molecules which are critical in presenting antigens to cytotoxic T cells [100]. This increases the visibility and recognitability of tumor cells to the immune system. Consequently, immune checkpoint inhibitors are more likely to attack tumors, which were previously perceived as non-immunogenic or resistant to immune checkpoint inhibitors. This epigenetic restructuring promotes the success of immunotherapy based on immune-checkpoint blockers, including anti-PD-1 and anti-PD-L1 antibodies [101]. Preclinical research and clinical trials in progress have indicated that the combination of DNMT and HDAC inhibitors and immune checkpoint inhibitors can result in enhanced, long-lasting, and systemic immune anti-tumor responses. Such a combination therapy is a promising modality of therapy in overcoming resistance, as well as enhancing outcomes in patients with different cancers [102].

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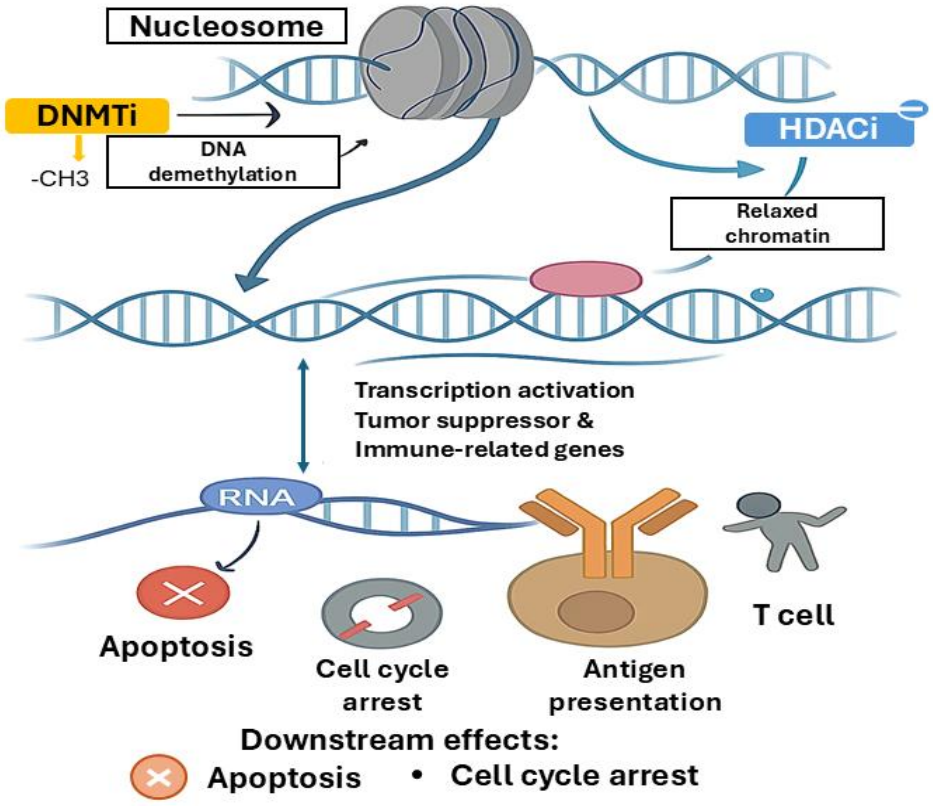


**Figure 2:** Molecular Crosstalk Between DNMT and HDAC Inhibition in Tumor Cells

## 6. Future Perspectives and Challenges

### 6.1. Selective Inhibitors

More effort is currently being directed towards the development of highly selective inhibitors of individual epigenetic enzymes, including isoform-selective HDACs, HMT's and DNMT's. Currently available epigenetic drugs that have been clinically approved are primarily broad-spectrum agents, meaning that they change several enzyme families at the same time. Although this can have a therapeutic effect in certain instances, it also poses a wide-ranging potential to cause off-target effects, undesirable changes in gene expression and also toxicity to normal tissues which eventually result in dose-limiting adverse events. Hence, it is necessary to create next-generation inhibitors that would possess a better level of specificity. More precise control of cancer-related gene expression and sparing of healthy cells by the selective targeting of individual HDAC, HMT, or DNMT isoforms

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can be expected to result in more effective and tolerable therapy.

### 6.2. Biomarkers

Proven predictive biomarkers are essential in order to maximize clinical use of epigenetic therapies. Biomarkers make it possible to identify patients who are most likely to respond to specific epigenetics drugs, which promotes a personalized and rational treatment. They can be DNA methylation, the histone modification pattern, non-coding RNA, or gene expression biomarker of drug response or resistance. Such molecular markers can improve the therapeutic outcomes, reduce the unnecessary treatment exposure, and facilitate the use of precision oncology, which can be incorporated into clinical decision-making. Continued studies are still essential in coming up with credible biomarker based models.

### 6.3. Resistance Mechanisms

The investigation of resistance mechanisms to epigenetic therapy is crucial to enhancing better clinical outcomes in the long term. The possibility of resistance can be the mutation of epigenetic regulators, the change in drug-binding affinity, the compensation of activating signalling networks, or significant rearrangements of the chromatid that do not allow the reactivation of therapeutic genes. The recognition and definition of these pathways will facilitate the rational design of combination therapy and new inhibitor specific to prevent or overcome resistance.

### 6.4. Epigenome Editing

The advent of technology, specifically CRISPR/dCas9 based engine, has presented new possibilities in regards to the editing of the epigenome with precision. Epigenome editing tools can be designed to exert epigenetic effects on a particular set of loca and not on the underlying DNA sequence, unlike the current epigenetic drugs, which have systemic action. This is the precision that has a lot of potential in the form of both permanent and highly discriminate therapeutic interventions.

### 6.5. Personalized Medicine

The creation of personalized cancer treatment by integrating personal tumor-specific epigenomic profiles into clinical practice is an important step in the right direction. Clinicians can use patient-specific DNA methylation profiles, histone-codes and transcriptional signatures to personalize epigenetic treatments to enhance therapeutic benefit and reduce toxicity. With the advancement of research, individualized epigenetic therapy is likely to make a great difference in terms of treatment accuracy and clinical effectiveness.

## 7. Conclusion

Epigenetic dysregulation is increasingly recognized as a fundamental hallmark of cancer, playing a critical role in abnormal gene expression, silencing of tumor suppressor genes, and driving uncontrolled cellular proliferation. Unlike genetic mutations, epigenetic alterations such as changes in DNA methylation, histone modifications, and chromatin remodelling are potentially reversible. This makes them

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attractive and promising targets for therapeutic intervention. Epigenetic therapies, particularly inhibitors targeting DNA methyltransferases (DNMTs) and histone-modifying enzymes like histone deacetylases (HDACs) and histone methyltransferases, have demonstrated substantial success, particularly in hematologic cancers such as myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML). These therapies can restore normal gene expression, promote cellular differentiation, and induce apoptosis in cancer cells. Furthermore, emerging studies highlight the potential application of epigenetic therapies in solid tumors, either as monotherapy or in combination with chemotherapy, targeted agents, or immunotherapies to enhance treatment efficacy and overcome drug resistance. However, optimizing their clinical utility requires continued progress in the identification of predictive biomarkers, personalized treatment strategies, and the design of robust clinical trials. Advancements in drug development and mechanistic understanding will further enhance their effectiveness and safety profiles. Ultimately, the integration of epigenetic therapies into standard cancer treatment holds great promise for improving patient outcomes and achieving more durable responses.

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