Explore the Advancements and Real-World Uses of DNA Methyltransferase and Histone Deacetylase Inhibitors in Clinical Settings

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Abstract

Epigenetic changes, such as DNA methylation and histone acetylation, are essential for controlling gene expression, cellular specialization, and the onset of several diseases like cancer. In recent years, there has been significant interest in the development of DNA methyltransferase and histone deacetylase inhibitors as potential therapeutic agents for the treatment of cancer and other diseases. These inhibitors work by targeting specific enzymes involved in epigenetic modifications, thereby modulating gene expression patterns. DNMT inhibitors, such as azacitidine and decitabine, are approved for myelodysplastic syndromes and acute myeloid leukemia treatment. HDAC inhibitors like vorinostat and romidepsin show promise in treating cutaneous T-cell lymphoma and other hematological malignancies, and can be used in combination therapy with other anticancer drugs. Furthermore, current research is dedicated to discovering new DNMT and HDAC inhibitors and investigating their potential uses in various cancer types and other medical conditions. The expansion of development and clinical trials for these compounds provides optimism for enhanced treatment choices and personalized medical approaches.

Keywords: *Gene expression, leukemia, hematological malignancies, anticancer, epigenetic, etc.*

Introduction

DNA methyltransferase and histone deacetylase inhibitors are a type of epigenetic medications that have displayed potential in cancer therapy [1]. Epigenetic alterations, particularly DNA methylation and histone acetylation, play a crucial role in regulating gene expression and maintaining cellular characteristics. In cancer, these changes are frequently disrupted, leading to modified expression of genes associated with tumor formation and suppression [2].

Compounds like azacytidine and decitabine function as DNMT inhibitors by targeting the process of DNA methylation [3].

This process typically involves adding a methyl group to cytosine residues on the genome's 5' carbon, resulting in gene silencing [4]. By integrating into DNA strands during replication, DNMT inhibitors trap DNMTs over time, ultimately leading to demethylation of DNA. This can lead to re-activation of previously silenced genes such as tumor suppressor genes which may impede the growth of certain cancers including hematological malignancies [5].

HDAC inhibitors work by suppressing enzymes called histone deacetylases which remove acetyl groups from lysine residues on histones causing chromatin to become more compacted thereby reducing gene expression levels [2]. Blocking these enzymes can result in relaxation of chromatin structure promoting activation of genes known for restraining tumor development [6]. Vorinostat and romidepsin are among approved HDAC inhibitors used against specific cancers such as cutaneous T-cell lymphoma (Tiffon et al., 2011; Prince & Dickinson, 2012). Both types have been extensively studied through clinical trials both alone or combined with other therapies. With growing understanding about epigenetics within different cancer types there is increasing potential for personalized use contributing toward improved cancer treatment options.

DNA methyltransferase inhibitors

DNA methyltransferases (DNMT) inhibitors are a type of medication that bocks the function of DNA methyltransferases, which are enzymes that add methyl groups to DNA. This methylation usually leads to the suppression of gene activity [9]. By hindering this process, DNMT inhibitors can reactivate silenced genes, making them crucial for the treatment of various illnesses, especially cancers.

Mechanism of Action of DNMT inhibitors

DNA methyltransferases (DNMTs) are enzymes responsible for adding methyl groups to the DNA molecule, typically at the cytosine bases within CpG dinucleotides. Main DNMTs are : DNMT1, DNMT3A, DNMT3B [10]. This methylation process leads to the gene silencing and plays a crucial role in gene expression regulation. DNMT inhibitors act by blocking the activity of DNMTs, thereby preventing the methylation of DNA. This inhibition can lead to the reactivation of previously silenced genes, which is particularly valuable in cancer therapy where tumor suppressor genes are often silenced through hypermethylation.

Key Mechanisms

1. **Covalent Binding and Degradation:** DNMT inhibitors, especially nucleoside analogs like 5-azcytidine and decitabine, incorporate into DNA during replication. These analogs covalently bind to DNMTs, leading to their degradation and reduction in cellular DNA methylation levels [11].
2. **Formation of DNMT-DNA Adducts:** At high doses, DNMT inhibitors form covalent DNMT-DNA adducts in aza-containing DNA, resulting in DNA damage and induces cell death, a crucial mechanism for their antitumor effects [12].
3. **Gene Reactivation:** By inhibiting DNMTs, these inhibitors facilitate the re-expression of genes silenced by methylation. For instance, they can restore the expression of MIG-6 by inhibiting of its promotor, playing a role in negative feedback regulation of gene expression [13].

4. **Impact on T cell Differentiation:** DNMT inhibitors also influence the immune system by preventing the differentiation of T-lymphocytes into regulatory T cells, thereby boosting antitumor immunity. This is accomplished by regulating the expression of gene such as Foxp3 [14].

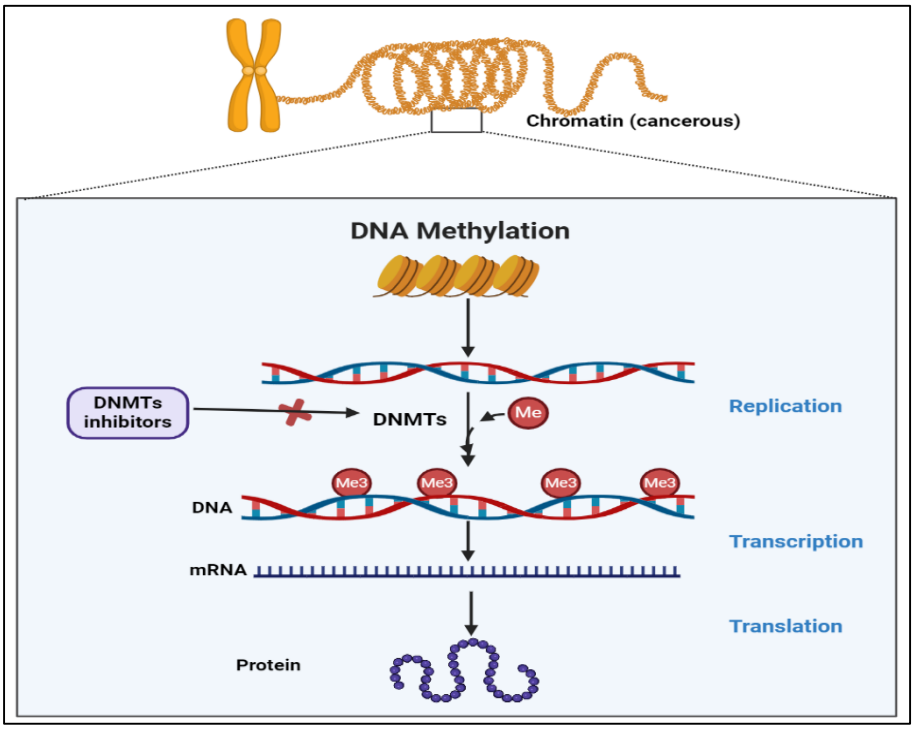

Figure 1. Mechanism of DNMTs inhibitors

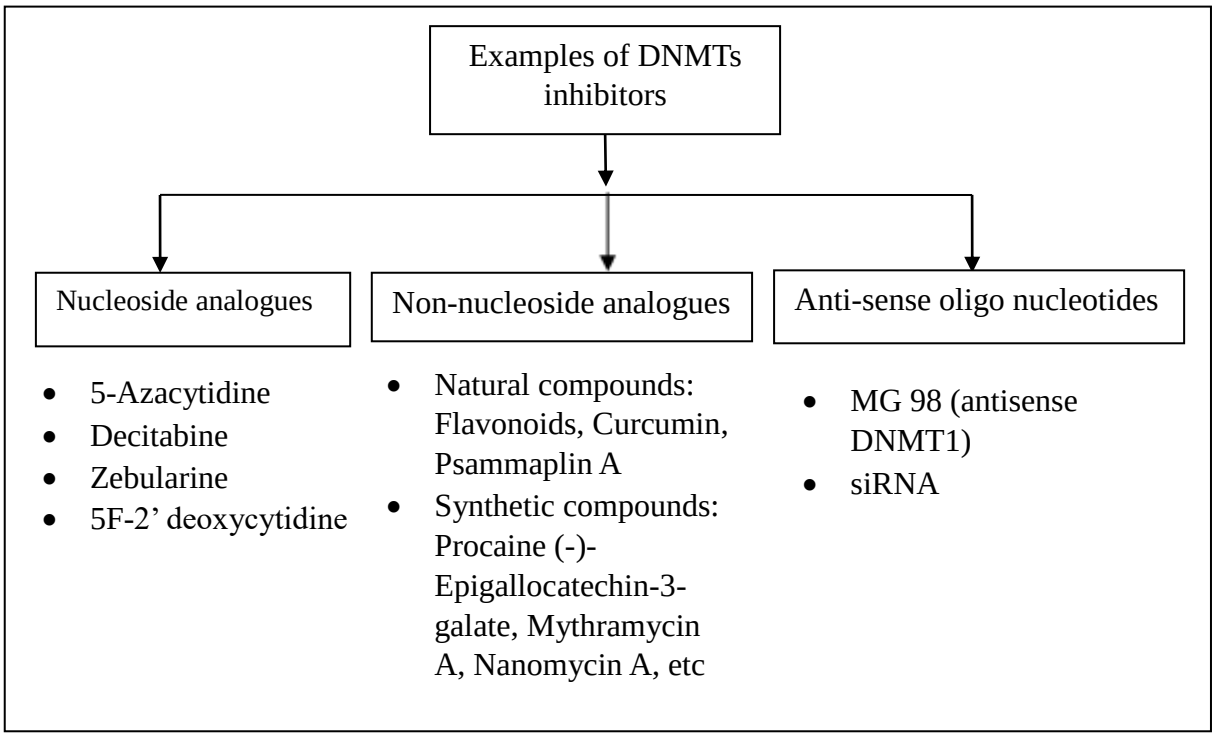

Figure 2. Classification of DNMTs inhibitors

1. **Cancer treatment:**

- **Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML):** Azacitidine and decitabine are FDA approved treatments for MDS and AML, significantly enhancing patient survival and quality of life. These drugs work by demethylating tumor suppressor genes, which reactivates pathways that regulate cell growth and apoptosis [15] [16].
- **Solid Tumors:** Recent research has investigated the use of DNMT inhibitors alongside other treatments for solid tumors like lung and breast cancer, showing improved therapeutic outcomes [17].

2. **Immunotherapy Enhancement:** DNMT inhibitors have shown potential in enhancing tumor immunotherapy by reactivating immune-related genes, thereby improving the immune system's ability to target cancerous cells [11].
3. **Combination Therapies:** DNMT inhibitors, when combines with HDAC inhibitors or immune checkpoint inhibitors, have demonstrated synergistic effects in both preclinical and clinical trials, boosting antitumor responses [16].

Recent Advances of DNMT inhibitors

1. **Novel DNMT Inhibitors:** Scientists are increasing the structural variety of DNMT inhibitors to tackle resistance and boost effectiveness. This includes crafting new molecules that target DNMT with greater selectivity and potency [18].
2. **Combination Therapies:** There is a rising trend in combining DNMT inhibitors with other cancer treatments to amplify anti-tumor effects. For instance, pairing DNMT inhibitors with immune checkpoint inhibitors has shown promise in early studies [19].
3. **FDA-Approved Treatments:** The FDA has approved two DNMT inhibitors, azacytidine (Vidaza) and decitabine, which are used for treating specific blood cancers. These approvals pave the way for developing more advanced DNMT inhibitors [20].
4. **Advance Assays:** Recent improvements in assay technologies have enhanced the screening and evaluation process of DNMT inhibitors, aiding the discovery of more effective compounds [11].

Histone Deacetylase Inhibitors (HDAC Inhibitors)

Histone deacetylase are the crucial regulators of gene expression by modifying histone proteins, which affect the chromatin structure and accessibility of DNA for transcription. Histone deacetylase inhibitors (HDACis) are the compounds that target histone deacetylase enzyme (HDAC).

Mechanism of HDAC inhibitors

By inhibiting the activity of HDAC, these inhibitors increase histone acetylation levels, leading to changes in gene expression patterns [21]. Thus having therapeutical potential in diseases like cancers, where they can induce cell cycle arrest, apoptosis, and differentiation in cancer cells [22].

Key mechanism of HDAC inhibitors

1. **Blocking HDAC Enzymes:** HDAC inhibitors directly impede HDAC enzymes activity, preventing the removal of acetyl groups from histone proteins [23].
2. **Increasing Histone Acetylation:** By hindering HDACs, HDACis raise the level of histone acetylation. This loosens the chromatin structure, thereby making the DNA more accessible to transcription factors and RNA polymerase [21].

3. **Modulating Gene Expression:** The increased acetylation of histone leads to changes in gene expression patterns. This process activates tumor suppressor genes and other genes that regulate cell cycle arrest, apoptosis, and differentiation, particularly in cancer cells [24] [25]. HDACis indirectly inhibits the HAT enzymes which leads to upregulation of transcriptional activation of tumor suppression genes, results in cell growth arrest and apoptosis [26].

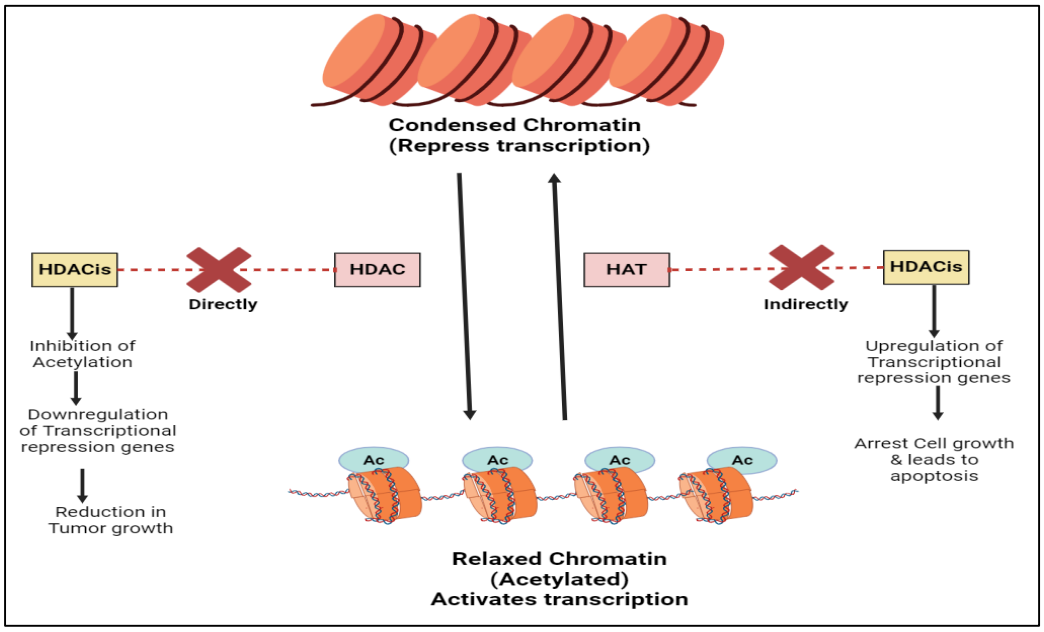

Figure 3. Mechanism of Histone deacetylase inhibitors (HDACis)

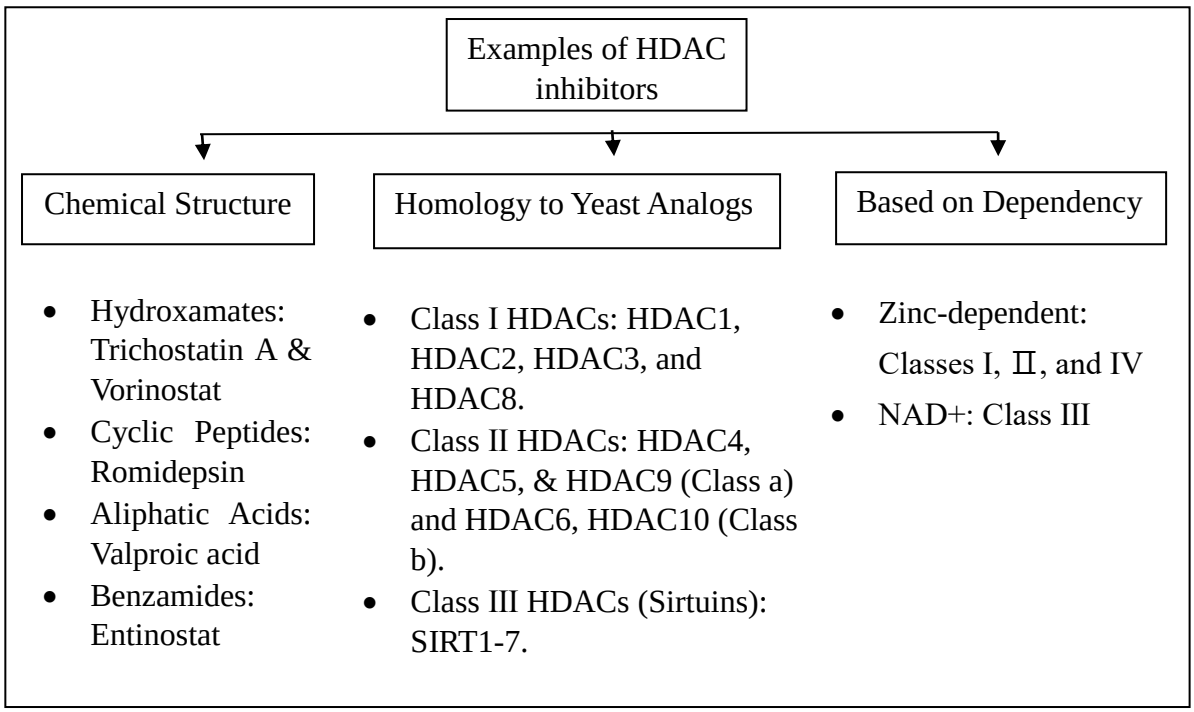

Figure 4. Classification of HDAC inhibitors (HDACis)

Clinical Applications:

1. **Cancer Treatment:**

- **Multiple Myeloma:** HDAC inhibitors like Vorinostat (SAHA) have been used to treat multiple myeloma by inducing apoptosis and inhibiting cell proliferation [27].
- **Solid Tumors and Hematologic Malignancies:** They are effective against a variety of cancers by reversing epigenetic modifications that promote tumor growth [28].

2. **Neurological Disorders:**

- **Epilepsy:** some HDAC inhibitors have shown potential in reducing seizure frequency and severity [28].
- **Spinal Muscular Atrophy and Huntington's Disease:** These are being investigated for their neuroprotective properties and ability to enhance gene expression that can mitigate these conditions [28].

3. **Other Diseases:**

- **Cystic Fibrosis:** HDAC inhibitors can restore the function of the CFTR protein, improving symptoms [28].
- **Inflammatory Diseases:** They are explored for their anti-inflammatory effects, which can be beneficial in conditions like rheumatoid arthritis [29].

4. **Combination Therapies:** HDAC inhibitors are often used in combination with other treatments to enhance efficacy and overcome drug resistance in cancer and other diseases [30].

Recent Advances of HDAC inhibitors:

1. **Expanded Clinical Trials:** All approved HDAC inhibitors are currently being investigated in clinical trials for additional types of neoplastic conditions, aiming to extend their therapeutic applications beyond their approved indications [30].
2. **Antitumor Effects:** Preclinical studies have demonstrated the effectiveness of various HDAC inhibitors in targeting HDACs to suppress tumor growth and progression, showcasing their potential in oncology [31].
3. **Selective Inhibition:** Recent research has focused on discovering new inhibitors that selectively target specific HDAC enzymes associated with particular disorders, such as T-cell lymphoma and childhood cancers. This selectivity aims to enhance efficacy and reduce side effects [32].
4. **HIV Treatment:** Advances in the structure-activity relationships of HDAC inhibitors have contributed to achieving HIV latency reversal, indicating potential uses beyond cancer treatment [33].
5. **Emerging Indications:** Investigating into HDAC inhibitors have revealed new indications and novel molecules that could offer improved therapeutic options for various diseases [30].

Conclusion

In summary, DNMT inhibitors offer a multifaceted approach, including the direct inhibition of DNA methylation, reactivation of silenced genes, and modulation of the immune response, making them powerful tools in cancer therapy. Histone deacetylase inhibitors (HDACis) are crucial in cancer therapy for their ability to regulate gene expression through histone acetylation modulation, inducing various beneficial effects in cancer cells. They also hold

promise for treating neurodegenerative and inflammatory diseases, expanding their therapeutic potential beyond oncology.

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