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# Modulators of DNA methylation and histone acetylation

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ABSTRACT

The distribution of epigenetic alterations, such as DNA methylation and histone modifications, is abnormal in cancer cells, and drugs that influence these changes are currently being used effectively in the treatment of hematopoietic malignancies. Two hypomethylating agents, 5-azacytidine and decitabine, are FDA-approved for the treatment of myelodysplastic syndromes, and one histone deacetylase inhibitor, vorinostat, was recently FDA-approved for patients with refractory cutaneous T-cell lymphoma. Generally, these agents are very well tolerated, with myelosuppression being the major side effect. Although they are thought to work by re-organizing chromatin to allow expression of genes silenced by DNA hypermethylation and repressive histone modifications, the precise mechanism of action of these agents is not yet clear. Current studies are examining the utility of these agents for the treatment of solid tumors as well as testing these drugs in combination to treat a variety of malignancies.



## 1. Introduction

In recent years, the clinical effectiveness of drugs that act on the epigenetic alterations present in cancer cells has been demonstrated in the treatment of several hematologic malignancies, including myelodysplastic syndromes, acute myeloid leukemias, and cutaneous T-cell lymphomas. These drugs work by a novel mechanism of action compared to traditional chemotherapy. In this review, we will summarize the clinical use of these agents in cancer treatment, focusing on recent developments in the field.

## 2. An overview of epigenetic changes in cancer

Within cells, DNA is organized into chromatin through binding of histone proteins that compact the DNA into nucleosomes [1]. Gene expression is regulated, in part, by chromatin structure and the ability of transcription factors and accessory proteins to gain access to promoter regions. Two epigenetic changes, DNA methylation and histone modifications, are heritable and affect gene expression, but do not alter the primary base sequence of DNA (Fig. 1). Other epigenetic changes occur within cells, but this review will focus on DNA methylation and histone alterations, since drugs that influence these processes have shown promise as anti-cancer therapies (Fig. 2).

DNA can be methylated at the 5-position of cytosine bases that are part of a 5′-CpG-3′ dinucleotide (Fig. 1 inset). Because a 5-methylcytosine base can deaminate spontaneously to form thymine, cytosine residues that are part of a CpG dinucleotide are sites of potential mutation and are under-represented in the genome. In fact, many of the C to T transition mutations found in the *TP53* gene occur at CpG dinucleotides [2]. CpG dinucleotides are concentrated in groups, called CpG islands, which often overlap the transcriptional start sites of genes.

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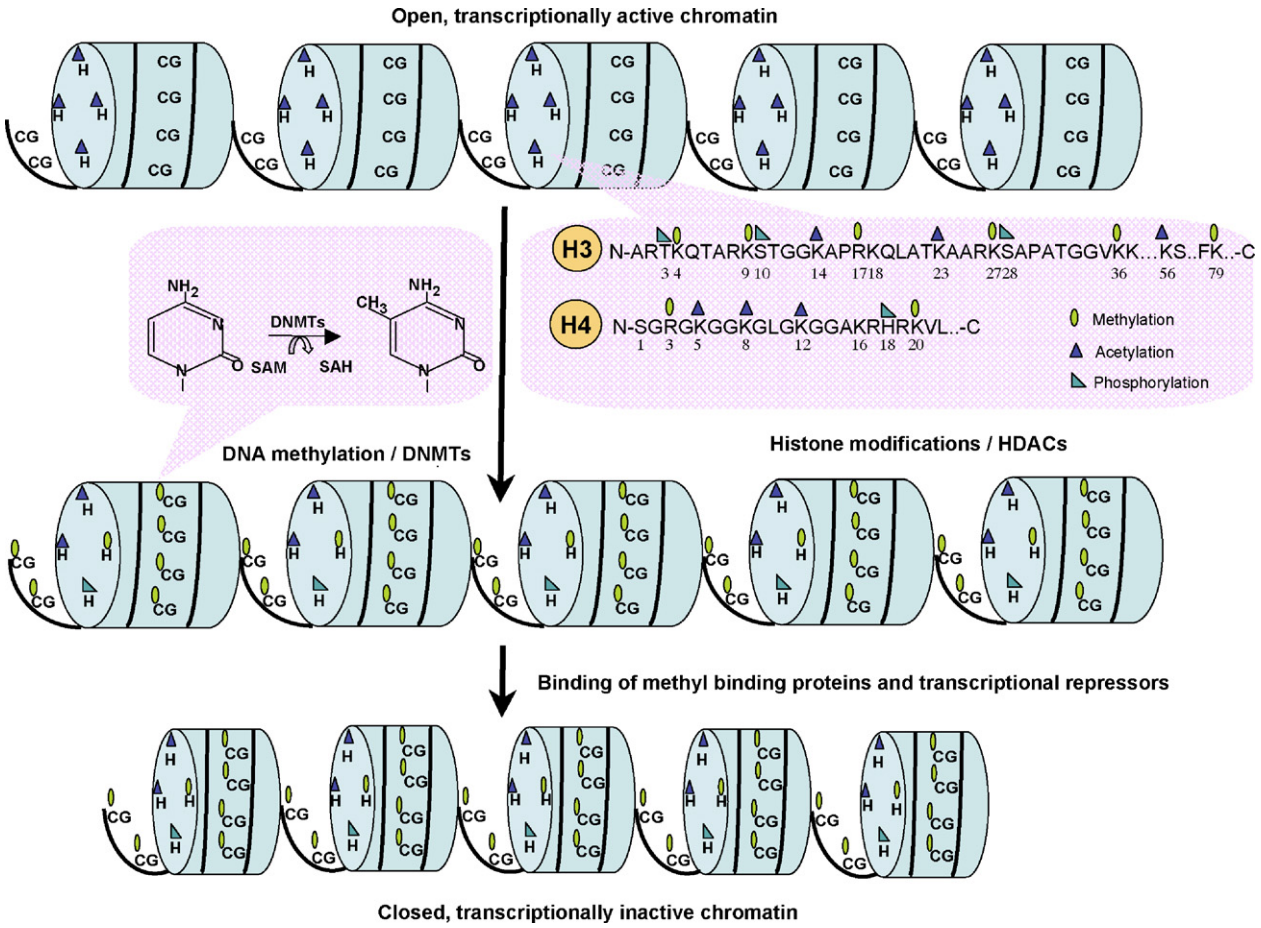


**Fig. 1 – DNA methylation and histone modifications alter chromatin structure and gene transcription. Trancriptionally active chromatin is characterized by highly acetylated histones (H) and unmethylated CpG dinucleotides (CG) as shown in the uppermost panel of the figure. Several enzymes modify chromatin in the transition from active to inactive chromatin states. DNA methyltransferase (DNMT) enzymes catalyze the DNA methylation reaction (shown in the bubble to the left), and histone deacetylase (HDAC) enzymes catalyze the deacetylation of histones. The DNMTs use S-adenylmethionine (SAM) as the methyl donor to add a methyl group to the 5-C of the cytosine group, generating S-adenosylhomocysteine (SAH). The bubble to the right illustrates many of the known histone modifications to histone H3 and H4. The one amino acid code is used to show the N-terminal sequence of each histone, and the amino acid number is indicated below. Well-characterized modifications of particular amino acids are shown: a green oval indicates methylation; a deep blue triangle indicates acetylation, and a light blue triangle indicates phosphorylation. Hypermethylation of CpG islands in some genes (e.g. tumor suppressor genes), removal of acetyl groups from histones by histone deacetylases (HDACs) and other enzyme modifications (methylation, phosphorylation, sumoylation) result in the recruitment of methyl binding proteins and transcriptional repressors. All of these changes result in the condensation of chromatin into a transcriptionally inactive state, depicted in the lowermost panel of the figure.**

Not every CpG in the genome is methylated. Highly methylated DNA is transcriptionally inactive, whereas hypomethylated DNA is associated with active, open chromatin (Fig. 1). In normal cells, repetitive DNA is highly methylated and thereby transcriptionally silenced, effectively inactivating transposable elements that could otherwise mediate genomic rearrangements. The density of DNA methylation within certain promoters contributes to their control, such that the promoters of transcribed genes are relatively hypomethylated compared to those of inactive genes.

In addition to DNA methylation, the transcriptional activity of DNA is controlled by histone modifications, including acetylation, methylation, phosphorylation, ubiquination, and sumoylation. DNA with highly acetylated histones is found as open chromatin, but underacetylated histones methylated at particular residues are found in a tightly wound, closed configuration that generally does not support transcription (Fig. 1). Often, combinations of histone modifications occur together to confer specific chromatin structures [3]. For example, histone H4 acetylated at K8 is found along with histone H3 modified at multiple sites (e.g. acetylation of K14 and phosphorylation of S10) in actively transcribed chromatin. Repressive chromatin, however, is characterized by deacetylated histones H3 and H4 and tri-methylation of histone H3 at K9. In addition, histone modifications can influence one another [4]. For example, methylation of histone H3 on K9