

Epigenetics can be defined as acquired changes in chromatin structure that arise independently of a change in the underlying DNA nucleotide sequence. Epigenetic modifications such as acetylation, methylation and ubiquitination can alter the accessibility of DNA to transcription machinery and therefore influence gene expression. The dysregulation of these epigenetic modifications has been shown to result in oncogenesis and cancer progression. The cell cycle, as well as proliferation and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are reversible and thus make promising therapeutic targets.

Epigenetic Mechanism

The fundamental unit of chromatin is the nucleosome, which consists of an octamer of the histone proteins H2A, H2B, H3 and H4 (two of each) tightly bound by DNA. Alterations in chromatin structure by post-translational modifications can regulate gene expression through the formation of heterochromatin or euchromatin, which usually repress or activate gene transcription, respectively. Post-translational modifications include DNA methylation and the covalent methylation (Me) and acetylation (Ac) of histone tails. DNA methylation represses transcription by blocking the binding of transcription complexes to the gene promoter. The acetylation of histone tails usually loosens the DNA from around the nucleosomes, increasing the accessibility of gene promoters to transcription complexes, therefore promoting transcription. Histone tail methylation can repress or promote gene expression, depending on the site and extent of methylation, as well as the presence of other histone modifications in the vicinity. The pattern of these post-translational modifications on a nucleosome determines the transcriptional profile of nearby genes. For example, the methyltransferase EZH2, part of the Polycomb Repressive Complex 2 (PRC2), represses its target genes through tri-methylation of lysine 27 on histone H3 (H3K27me3). The functions of histone ubiquitination are less well understood. However, increasing evidence points to an important role for this epigenetic modification in the DNA damage response.

Types of Epigenetic Modifiers

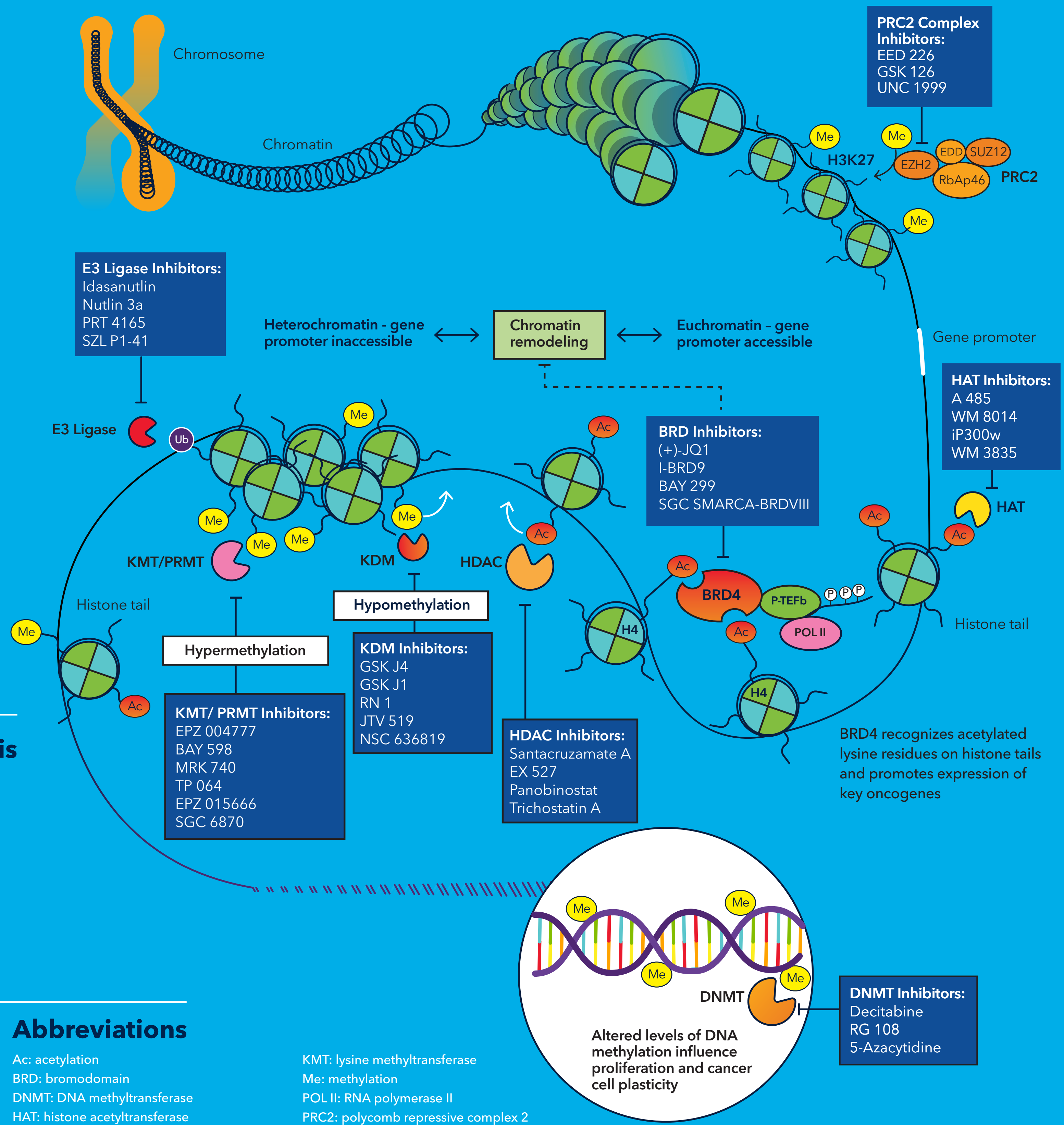
Proteins that carry out these epigenetic modifications can be thought of as being either “writers”, “readers” or “erasers”.

- Epigenetic writers catalyze the addition of epigenetic marks onto either histone tails or the DNA itself
- Epigenetic reader domains are effector proteins that recognize and are recruited to specific epigenetic marks. “Writer” and “eraser” enzymes may also contain such reader domains, leading to the coordination of “read-write” or “read-erase” mechanisms
- Epigenetic erasers remove epigenetic marks to alter gene expression

BRD Inhibition Suppresses Tumor Growth and Metastasis

Bromodomains (BRDs) are epigenetic “readers” that selectively recognize acetylated lysine residues on histone protein tails. Of particular interest is the BET (bromodomain and extra-terminal) bromodomain family, which comprises the ubiquitously expressed proteins BRD2, BRD3, BRD4; and the testis-specific protein, BRDT. BET proteins are epigenome readers that play a key role at the interface between chromatin remodeling and transcriptional regulation and are integral in the regulation of transcriptional elongation and the cell cycle. BRD4 influences mitotic progression and is a critical mediator of transcriptional elongation because it binds to transcriptional sites of genes expressed during the M/G₁ cell cycle transition. BRD4 increases expression of genes that promote growth by recruiting P-TEFb to mitotic chromosomes. Furthermore, it has been observed that BRD4 is significantly upregulated in both primary and metastatic melanomas. *In vivo* studies have shown that inhibition of BRD4 impairs tumor growth and metastasis. Key BRD4 inhibitors include the potent, high affinity and selective, archetypal BET bromodomain inhibitor (+)-JQ1, which induces squamous cell differentiation and arrests tumor growth in BRD4-dependent carcinomas, including tumor growth in midline carcinoma cell xenograft models. Small molecule “Degradors” (PROTAC®), such as MZ1 and dBET1, can be used for BRD4 Targeted Protein Degradation (TPD). MZ1 demonstrates a strong inhibitory effect on tumor growth and suppressed BRD4 expression in a mouse model of JQ1-resistant triple-negative breast cancer, while dBET1 induces BRD4 protein degradation resulting in antitumor efficacy in murine xenograft model of human leukemia cells.

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Abbreviations

- Ac: acetylation
 BRD: bromodomain
 DNMT: DNA methyltransferase
 HAT: histone acetyltransferase
 HDAC: histone deacetylase
 KDM: histone demethylase
- KMT: lysine methyltransferase
 Me: methylation
 POL II: RNA polymerase II
 PRC2: polycomb repressive complex 2
 PRMT: protein arginine methyltransferase
 P-TEFb: positive transcription elongation factor b
 Ub: ubiquitin

Tocris Products

- Bromodomains (BRD)**
 (+)-JQ1
 BAY 299
 BI 9564
 CeMMEC1
 dBET1
 FHT 1015
 FHT 2344
 GSK 6853
 I-BET 762
 iBET-BD2
 I-BRD9
 L Moses
 MZ 1
 NVS-CECR2-1
 NVS MLLT-1
 PFI 3
 SGC-CBP30
 SGC SMARCA-BRDVIII
 TP 238
 TP 472
- Pan-HDACs**
 Panobinostat
 SAHA
 Trichostatin A
- Histone Demethylases (KDM)**
 GSK J1
 GSK J4
 GSK LSD 1
 JQKD 82
 JTV 519
 NSC 636819
 RN 1
- Lysine Methyltransferases (KMT)**
 BAY 598
 BAY 6035
 BI 9321
 EPZ 004777
 MRK 740
- DNA Methyltransferases (DNMT)**
 5-Azacytidine
 Decitabine
 RG 108
 SGI 1027
- Polycomb Repressor Complex (PRC)**
 A 366
 EED 226
 GSK 126
 UNC 1999
- DNA-dependent Protein Kinases**
 AZD 7648
 KU 0060648
- Histone Acetyltransferases (HAT)**
 A 485
 iP300w
 NU 9056
 WM 3835
 WM 8014
- Histone Deacetylases (HDACs)**
Class I
 CI 994
 MS 275
 PCI 34051
 RGFP 966
 Santacruzamate A
- Class II**
 BRD 73954
 BRD 9757
 LMK 235
 Tubastatin A
- Class III**
 EX 527
 SirReal 2
 SRT 1720
- Poly (ADP-ribose) Polymerases (PARP)**
 AZD 2461
 GeA-69
 H10
 Olaparib
 Rucaparib camsylate
- Protein Arginine Methyltransferases (PRMT)**
 EPZ 015666
 GSK 591
 MS 023
 SGC 6870
 TP 064
- Protein Ser/Thr Phosphatases**
 GSK 2830371
- Ubiquitin E3 Ligases**
 Idasanutlin
 Nutlin 3a
 PRT 4165
 SZL P1-41
- WDR5**
 MM 102
 OICR 9429

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NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.



Wall Poster

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Epigenetics in Cancer

Epigenetic Mechanism

The epigenome is a dynamic and reversible system that regulates gene expression and cellular differentiation. It is composed of DNA and histone modifications that influence the accessibility of DNA to transcription factors and other regulatory proteins. Epigenetic changes can be inherited or acquired during an individual's lifetime, and they play a central role in the development and progression of cancer.

Types of Epigenetic Modifiers

Epigenetic modifiers are enzymes that catalyze the addition or removal of epigenetic marks. They are classified into two main groups: DNA methyltransferases (DNMTs) and histone modifiers. DNMTs are responsible for the addition of methyl groups to DNA, while histone modifiers are involved in the modification of histone tails, such as acetylation and methylation.

HDAC Inhibition Suppresses Tumor Growth and Metastasis

HDAC inhibitors (HDACi) are a class of epigenetic modifiers that block the activity of histone deacetylases (HDACs). By inhibiting HDACs, HDACi increase the levels of acetylated histones, which leads to a more open chromatin structure and increased gene expression. This mechanism of action makes HDACi a promising therapeutic approach for the treatment of cancer, as they can suppress tumor growth and metastasis by restoring the expression of tumor suppressor genes.

Abbreviations

HDAC: Histone deacetylase
DNMT: DNA methyltransferase
HDACi: Histone deacetylase inhibitor
DNMTi: DNA methyltransferase inhibitor

Toxic Products

Acute Toxicity: LD50 (mg/kg): 1000 (oral, rat); 100 (intraperitoneal, mouse)

Chronic Toxicity: No significant effects observed at doses up to 1000 mg/kg/day for 90 days in rats.

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