Epigenetics in Cancer

Adapted from Edition 3 of the Tocris Cancer Product Guide
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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 and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are considered to be reversible and thus make a promising therapeutic target.

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.

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

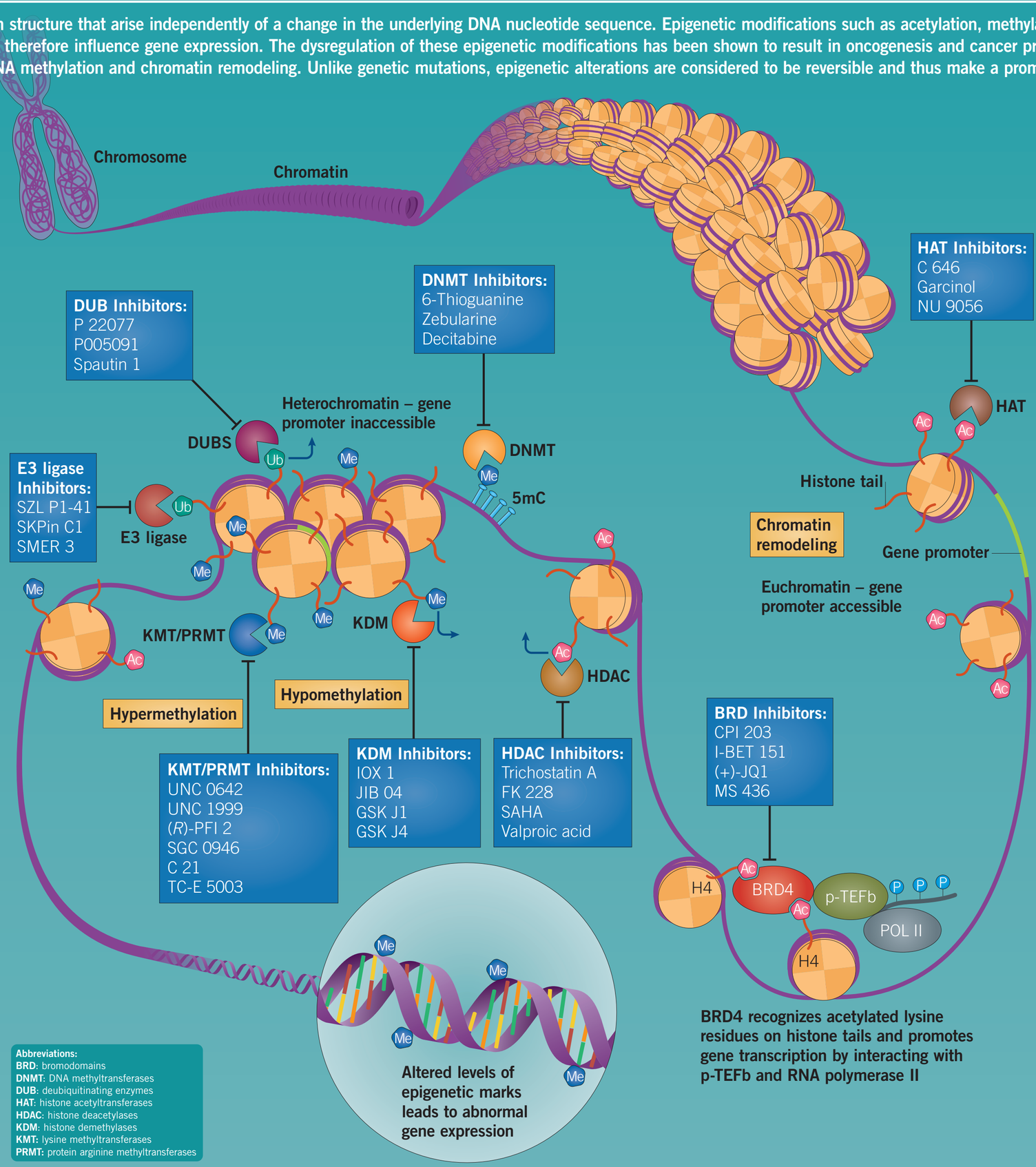
Proteins that carry out these epigenetic modifications can be thought of as being either "writers", "readers" or "erasers".

- **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/G_1 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, archetypical 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. I-BET 151 potently blocks recruitment of BRD3/4 to chromatin, inducing apoptosis and cell cycle arrest in MLL-fusion leukemia cell lines. This compound has also been shown to improve survival in rodent models of MLL-fusion leukemia.



Abbreviations:
BRD: bromodomains
DNMT: DNA methyltransferases
DUB: deubiquitinating enzymes
HAT: histone acetyltransferases
HDAC: histone deacetylases
KDM: histone demethylases
KMT: lysine methyltransferases
PRMT: protein arginine methyltransferases

Products available from Tocris

14-3-3 Proteins
Difopein

Aurora Kinases
Anacardic acid, CCT 137690, Hesperadin, PF 03814735, SNS 314, TC-A 2317, TC-S 7010, ZM 447439

Bromodomains (BRD)
BAZ2-ICR, CP 203, GSK 2801, GSK 5959, I-BET 151, I-BRD9, (+)-JQ1, MS 436, NI 57, OF 1

Deubiquitinating Enzymes
P 22077, P005091, Spautin 1

DNA Methyltransferases (DNMT)
5-Azacytidine, Decitabine, EGCG, RG 108, SGI 1027, 6-Thioguanine, Zebularine

Histone Acetyltransferases (HAT)
C 646, Garcinol, L002, NU 9056

Histone Deacetylases (HDAC)
FK 228, MC 1568, MI 192, PCI 34051, SAHA, Trichostatin A, UF 010, Valproic acid

Histone Demethylases (KDM)
GSK J1, GSK J2, GSK J4, IOX 1, JIB 04, RN 1, TC-E 5002

Lysine Methyltransferases (KMT)
A 366, EPZ 004777, (*R*)-PFI 2, SGC 0946, UNC 0642, UNC 1999

MBT Domains
UNC 1215, UNC 926

Poly (ADP-ribose) Polymerase (PARP)
BYK 204165, EB 47, JW 55, MN 64, Nicotinamide, NU 1025, PJ 34, TC-E 5001, WIKI4, XAV 939

Protein Arginine Methyltransferases (PRMTs)
C 21, TC-E 5003

Protein Ser/Thr Phosphatase
Ascomycin, GSK 2830371, Okadaic acid, Sanguinarine, Tautomycetin

Protein Tyrosine Phosphatase
Alexidine dihydrochloride, Sodium orthovanadate

RNA/DNA Polymerase
Mithramycin A, Thiolutin

Ubiquitin E3 Ligases
SZL P1-41, SKPin C1, SMER 3

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