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Epigenetics in Cancer

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.

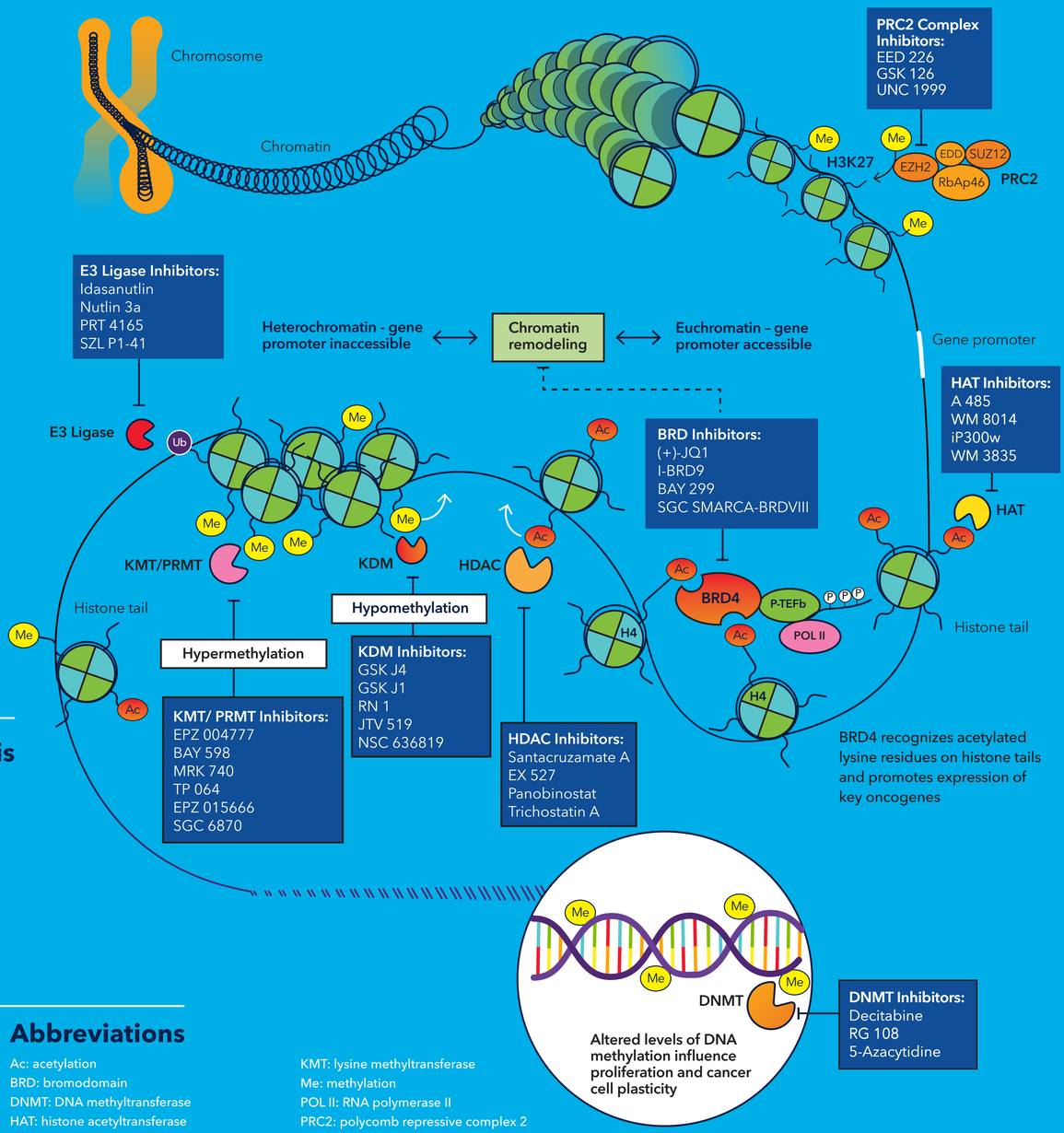
Types of Epigenetic Modifiers

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/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, 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 "Degraders" (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.



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

DNA Methyltransferases (DNMT)
5-Azacytidine
Decitabine
RG 108
SGI 1027

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

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

Polycomb Repressor Complex (PRC)
A 366
EED 226
GSK 126
UNC 1999

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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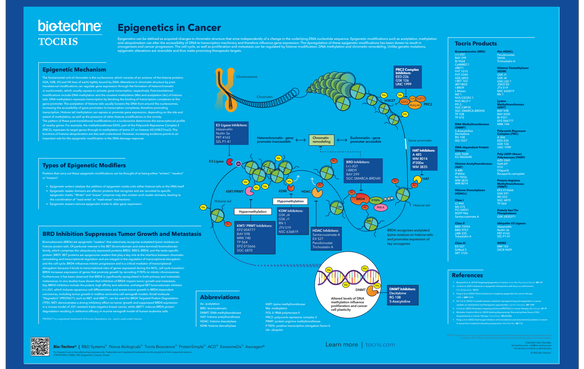

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