EPIGENETIC REPROGRAMMING

Anita Baillet, MCU
Faculty of Pharmacy
Paris-Saclay University

EPIGENETIC REPROGRAMMING

Epigenetics regulates gene expression without alteration of the DNA sequence

Inappropriate activation of oncogenes or inactivation of tumor suppressors

Misregulation of important pathways that control normal cellular homeostasis

cell cycle regulation, potential to repair DNA damage or to induce apoptosis, response to inflammatory stimuli, cell signaling, and cell growth control and differentiation

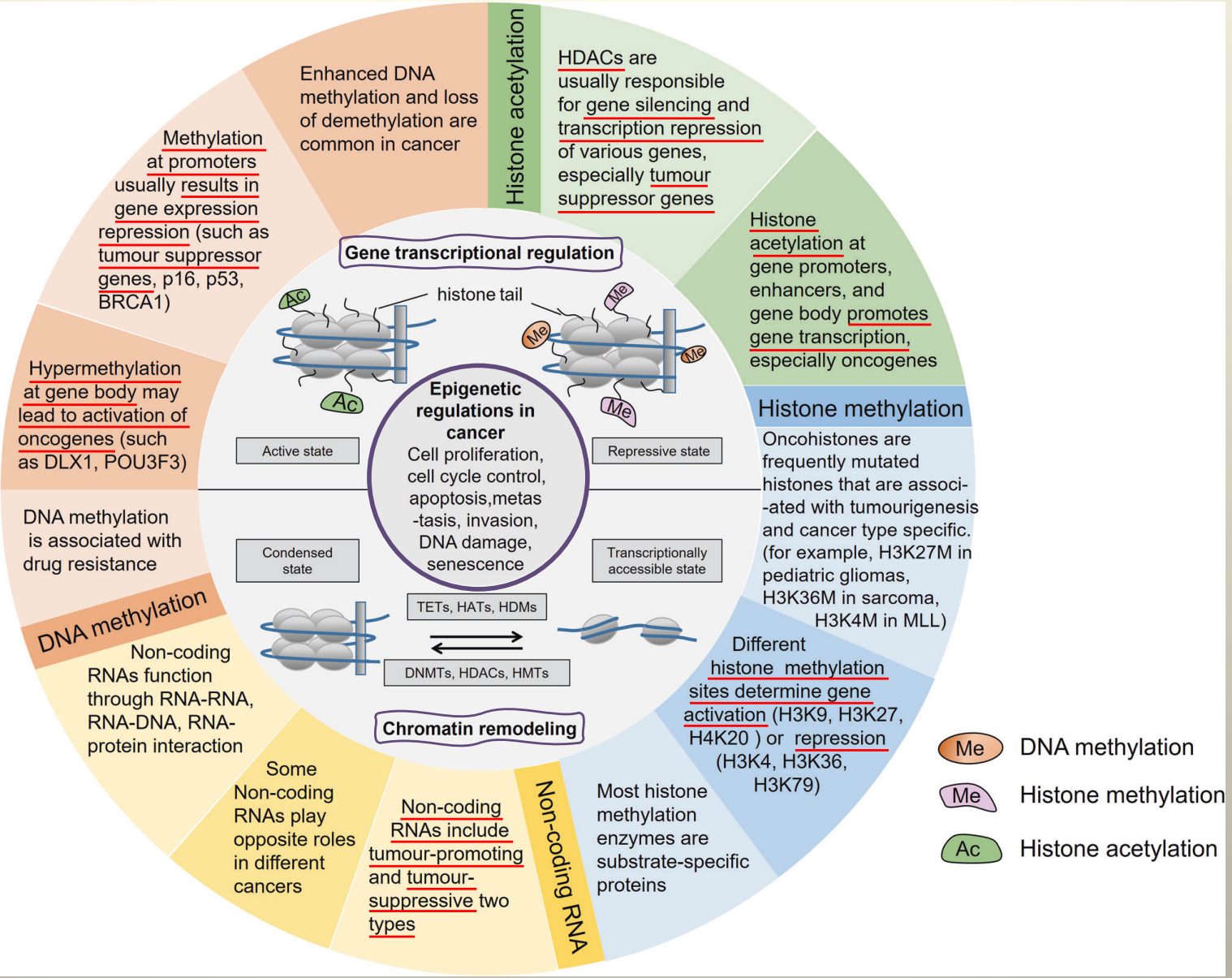
Epigenetic transcriptional control can occur through :

The epigenetic code

- ✓ DNA methylation
- ✓ Covalent histone modifications and chromatin remodeling *(mainly methylation and acetylation)*
- ✓ Noncoding RNAs

Development of epigenetic drugs applying to cancer therapeutics

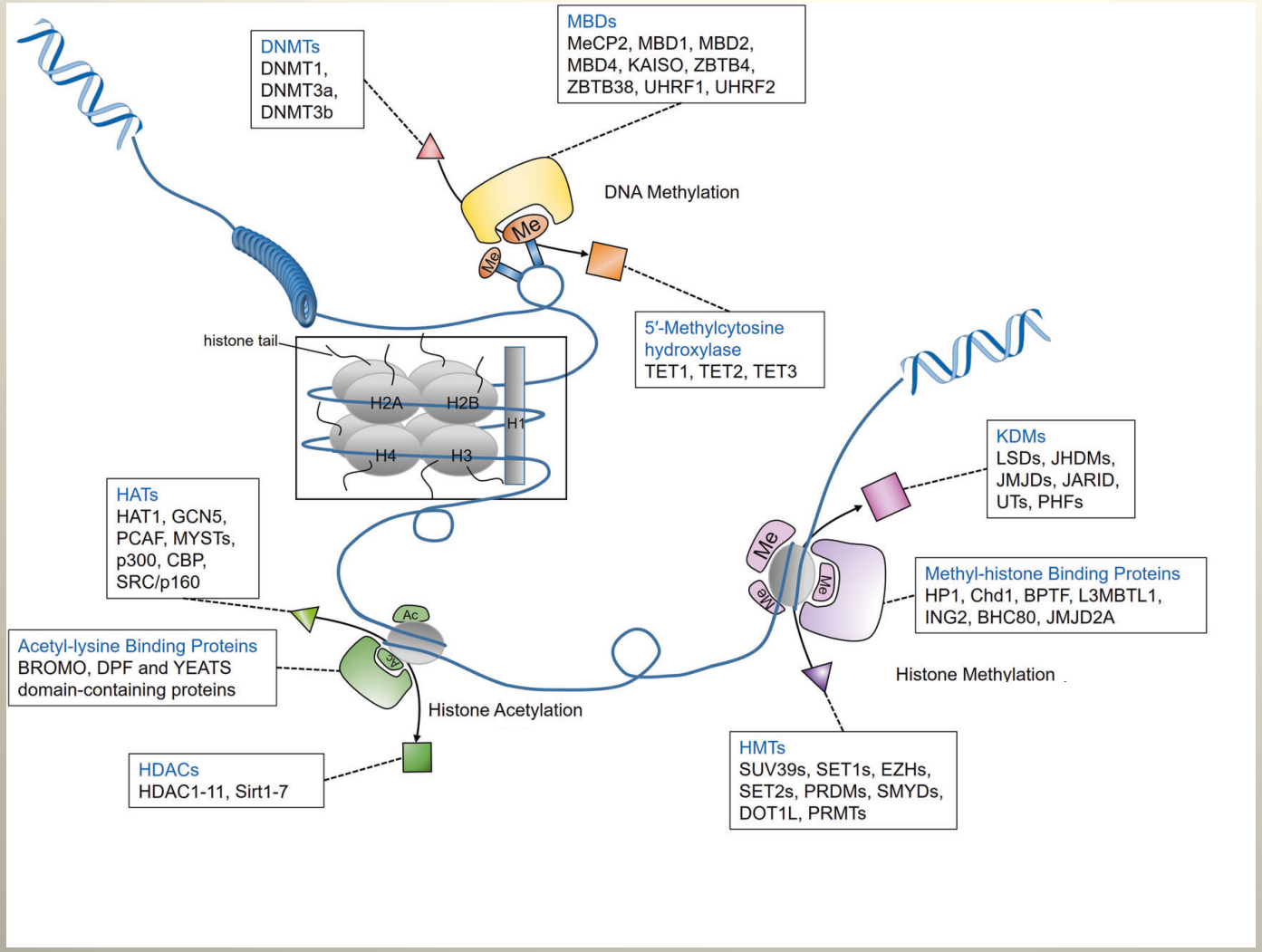
EPIGENETIC REPROGRAMMING



Cheng et al., Signal Transduction and Targeted Therapy 2019

EPIGENETIC REPROGRAMMING

DNA methylation Histone methylation Histone acetylation



Cheng et al., Signal Transduction and Targeted Therapy 2019

« Writers »

DNMTs DNMT1
HMTs SETD2, DOT1L
HATs CBP/p300

« Readers »

MBDs UHRF1
Other binding proteins
Bromodomain-containing proteins, BRCA1

« Erasers »

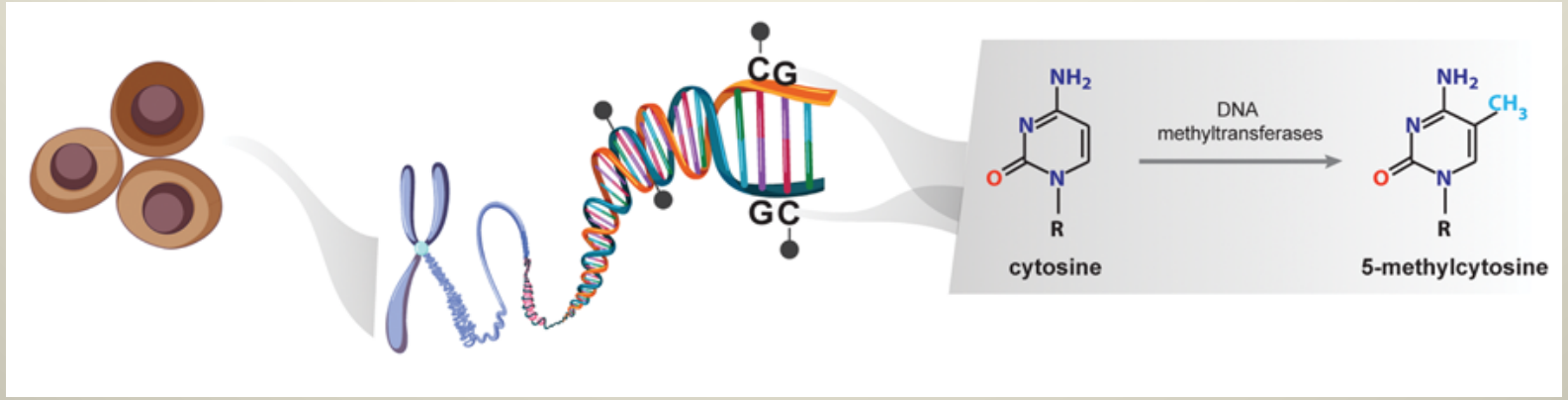
DNA-demethylating enzymes
TET1
KDMs LSDs
HDACs HDAC1, Sirt1

DNA methylation THE WRITERS

Discovered in the early 1980s

DNMTs DNA methyltransferases

Five members : DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L

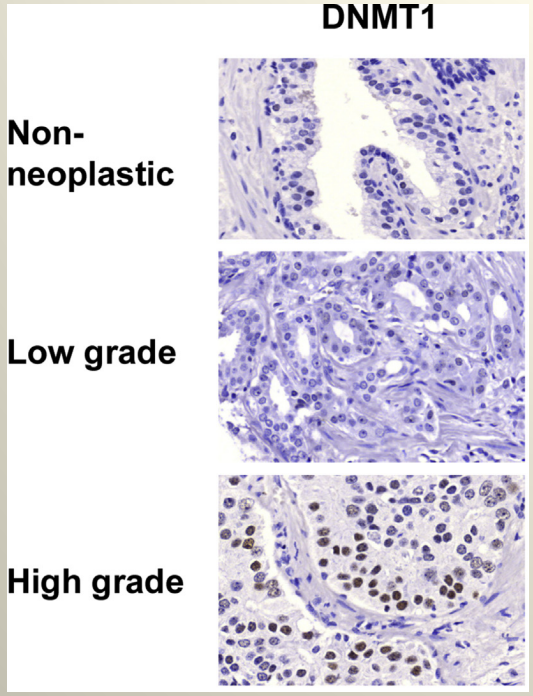


Skvortsova et al., Essays in Biochem 2019

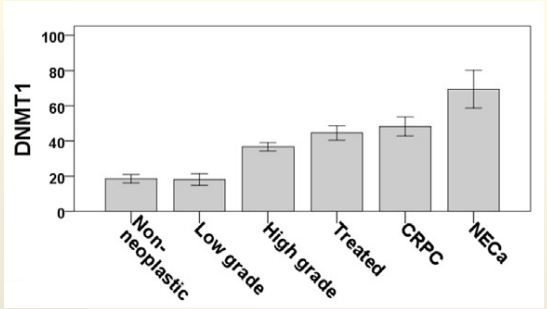
Catalyze the addition of a methyl group to the fifth carbon position of cytosines, especially at a C followed by a guanine (G), so-called CpG sites

Most abundant epigenetic modification with a crucial role in development and cellular biology
Overexpression of DNMT1, DNMT3a, and DNMT3b has been observed in multiple cancers

Nuclear expression of DNMT1

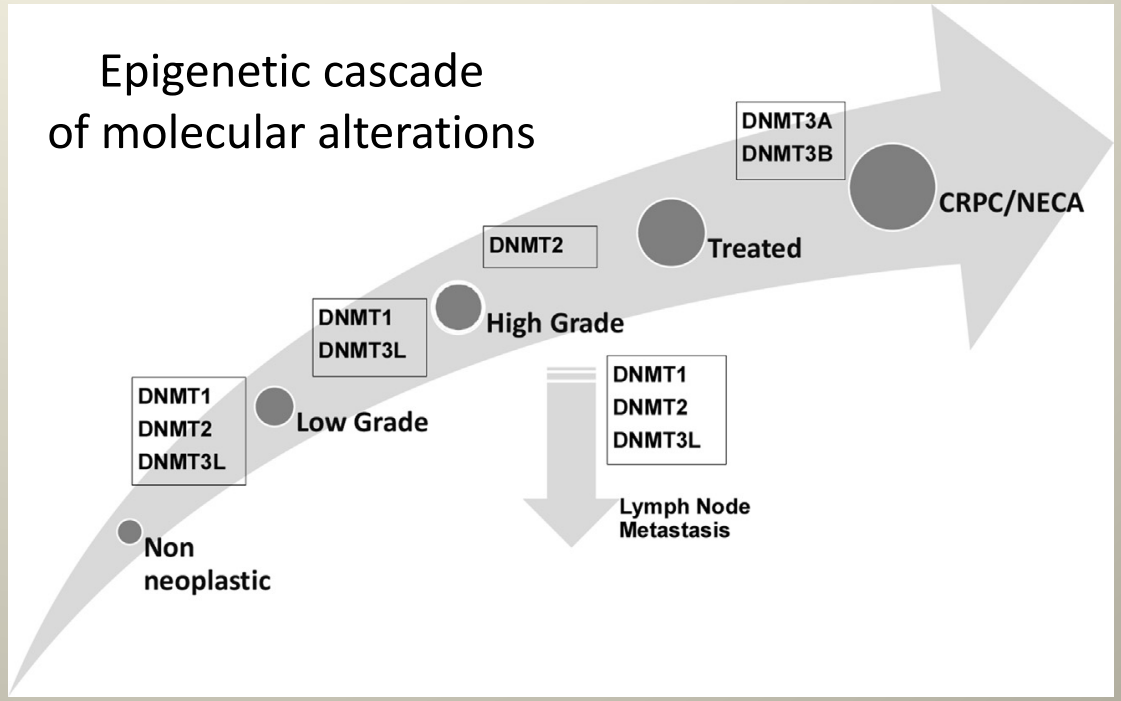


Immunohistochemistry



Prostate cancer

CRPC : castration resistant prostate cancer
NECa : neuroendocrine prostate cancer

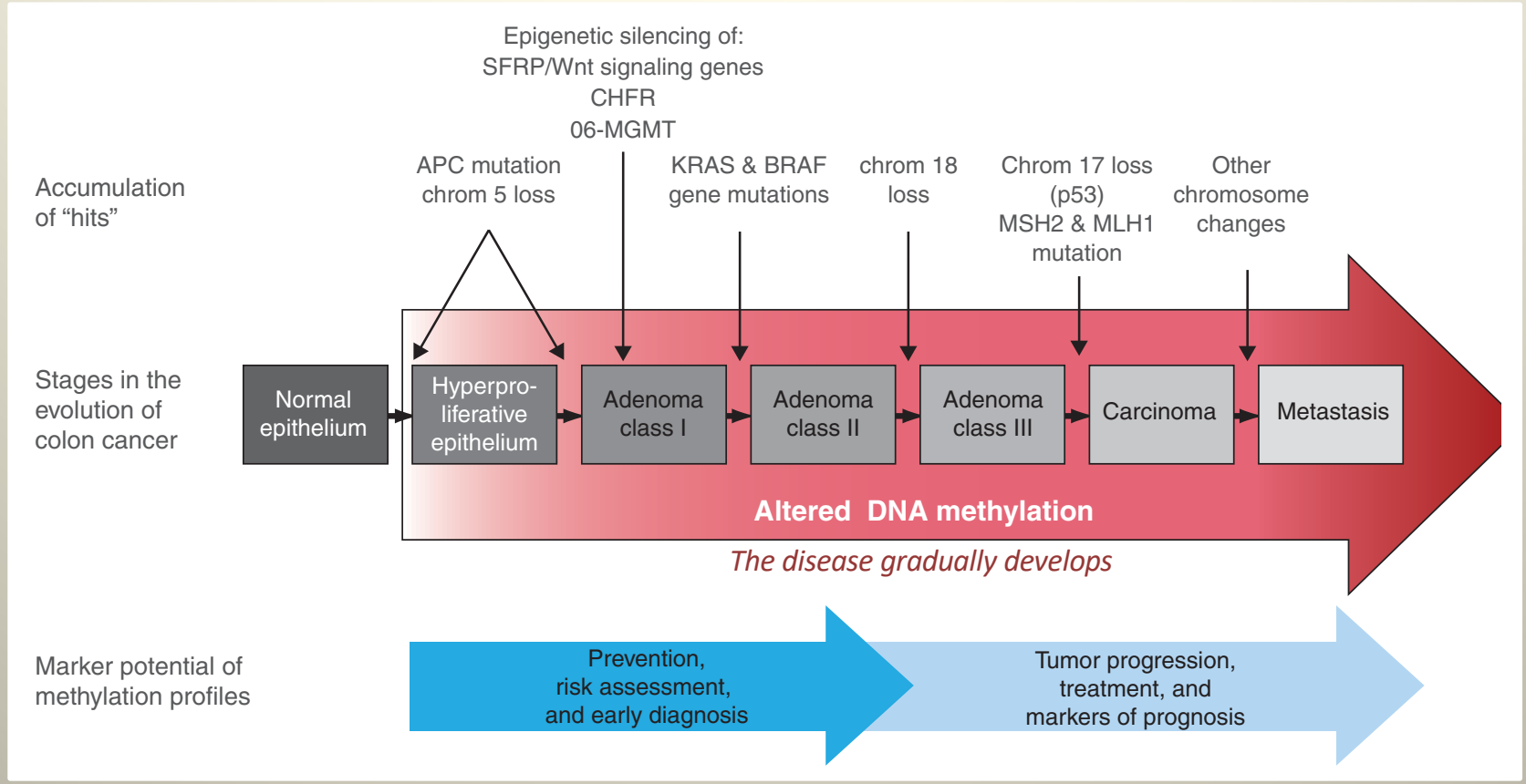


DNMT1, DNMT2 and DNMT3L may be associated with the emergence of PCa

Tzelepi et al., Anat. Pathol. 2020

Perturbation of DNA methylation

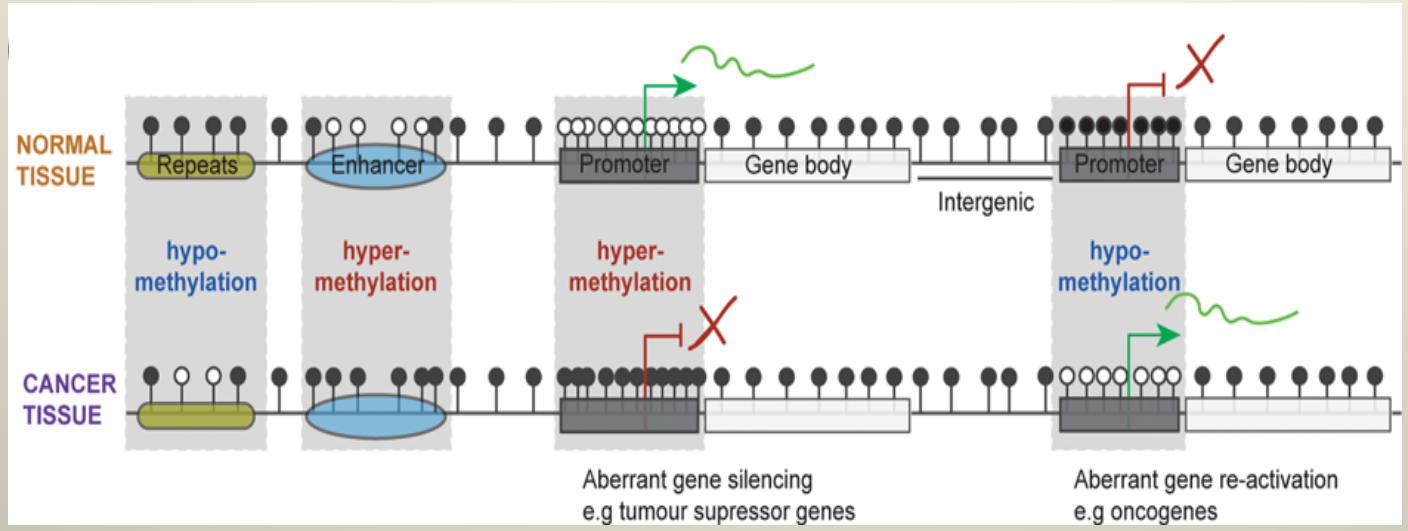
Classic model for sequential genetic alterations during the evolution of colon cancer



Kinzler and Vogelstein, 1997 *Baylin and Jones, Cold Spring Harb Perspect Biol 2016*

Perturbation of DNA methylation

Global loss of 5mC in cancer cells,
but abnormal presence of punctate increases in DNA methylation
across enhancers and promoters



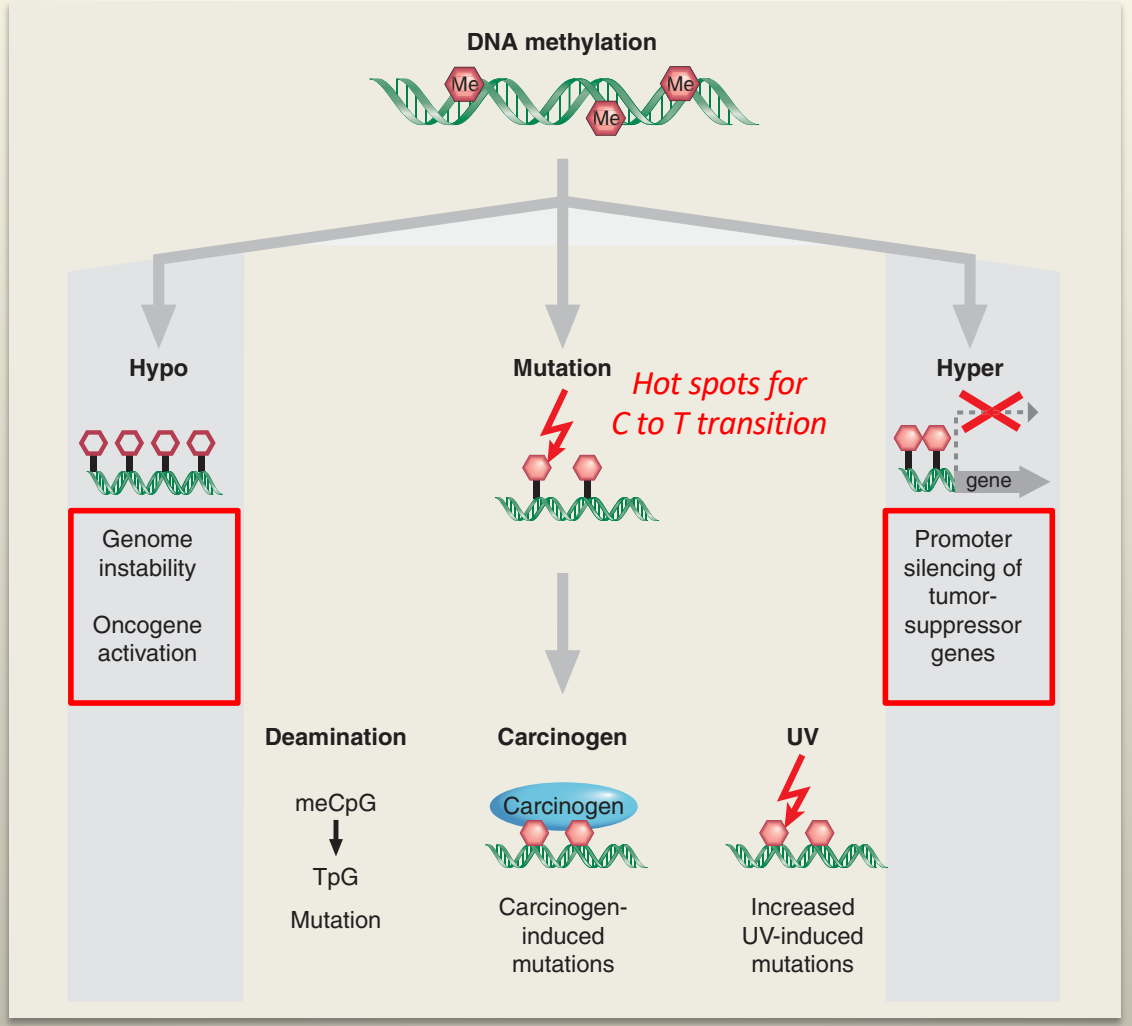
Skvortsova et al., Essays in Biochem 2019

⇒ *Transcriptional repression of tumor suppressor genes and concomitant increase in the expression of oncogenes*

The cyclin-dependent kinase inhibitor, p16, is silenced in many types of cancer by hypermethylation of a CpG island residing in its promoter, resulting in loss of cell cycle regulation and in a growth advantage to affected cells

Perturbation of DNA methylation

Three main consequences...



Baylin and Jones, Cold Spring Harb Perspect Biol 2016

Three methyl-CpG binding domain protein (MeCP) families can read the established methylated DNA sequences

- ✓ Methyl-CpG Binding Domain (MBD) proteins
- ✓ Zinc-finger and BTB domain-containing proteins

  KAISO (ZBTB33), ZBTB4 and ZBTB38, which bind to methylated DNA via zinc-finger motifs
- ✓ Two ubiquitin-like proteins with PHD and RING finger domains

  UHRF1 and UHRF2, which recognize 5-mC via RING finger-associated (SRA) domains

Methylation of DNA can also be a barrier for certain transcription factors to bind to promoter sites such as AP-2, c-Myc, CREB/ATF, E2F, and NF-kB

Role of UHRF1 in carcinogenesis

Ubiquitin-like, containing PHD (Plant HomeoDomain) and RING (Really Interesting New Gene) finger domains 1 (UHRF1)

Plays a key role in the maintenance of correct DNA methylation

Through the SRA domain,
UHRF1 interacts with HDAC1 and DNMT1

⇩

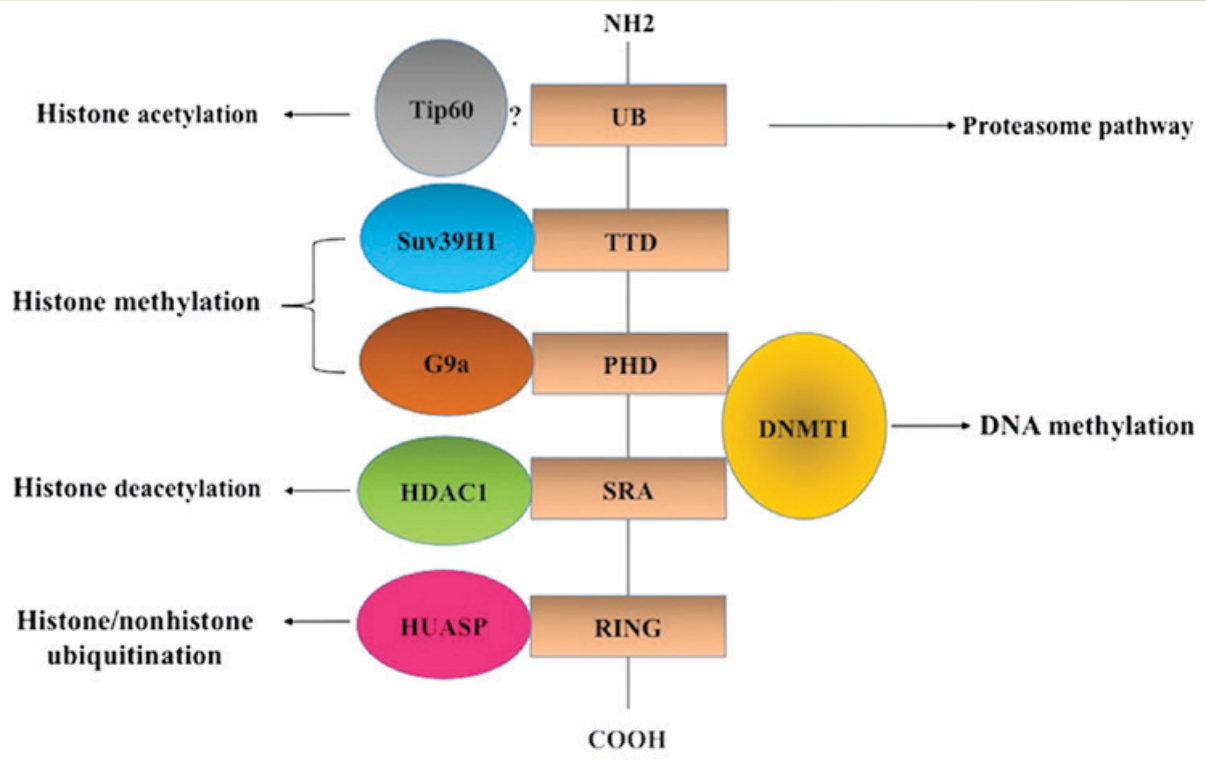
Coordinated crosstalk
Regulation of the epigenetic code

UHRF1 binds to H3K9me2/3

⇩

Additional evidence of
UHRF1-mediated crosstalk between
DNA methylation and histone modification

Schematic structure/function domains of UHRF1
involved in the epigenetic regulation of gene expression



Choudhry et al., Oncology Letters, 2018

Role of UHRF1 in carcinogenesis

Ubiquitin-like containing plant homeodomain (PHD) and really interesting new gene domain (RING) finger domains 1 (UHRF1)

Overexpressed in various human cancer cells

potential biomarker for the prognosis and diagnosis of several types of cancer

High expression of UHRF1

⇩

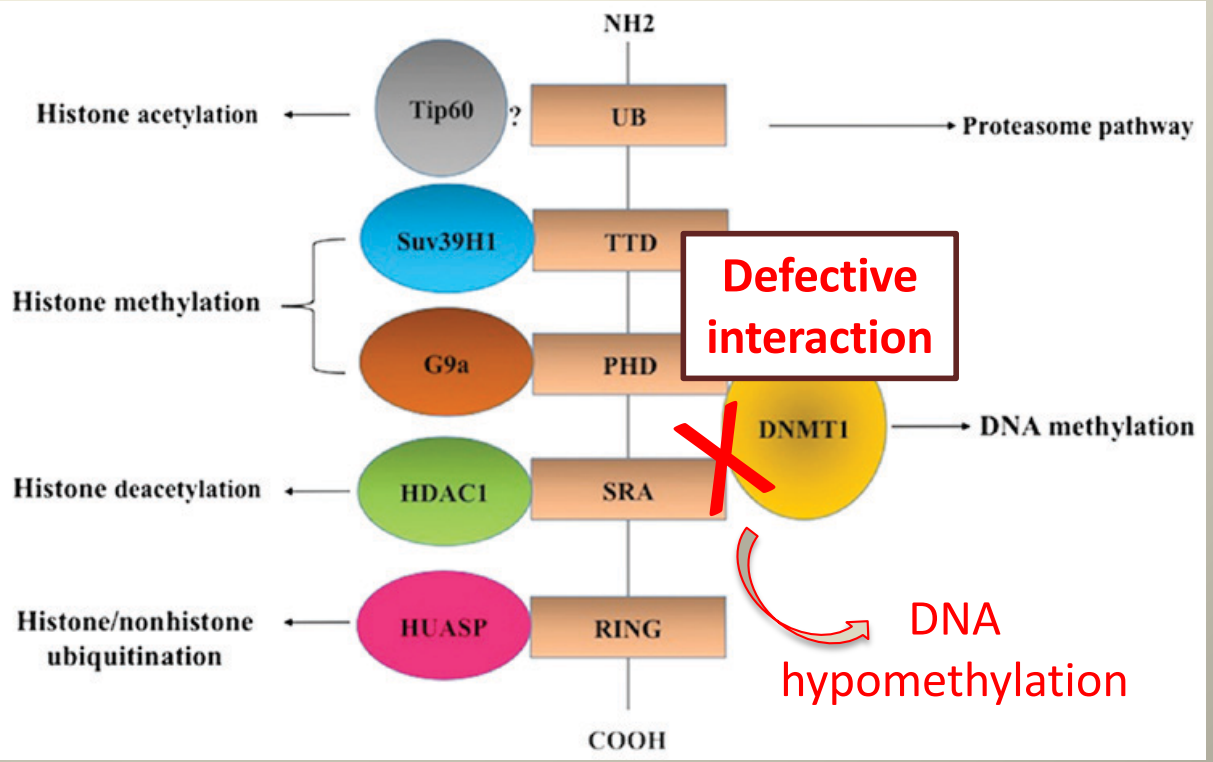
DNA hypermethylation

⇩

inhibits a variety of TSGs

participates in the occurrence, progression, and invasion of cancer

Schematic structure/function domains of UHRF1



Choudhry et al., Oncology Letters, 2018

Xue et al., OncoTargets &Therapy 2019

Perturbation of DNA methylation

Table 1 Inhibition of TSGs by overexpression of UHRF1 in various types of cancers

TSGs	Functions	Cancers
$P16^{INK4}$	Growth, metastasis, and apoptosis	Colorectal cancer [22219067] Cervical cancer [23688286] Glioblastoma [25550546]
BRCA1	DNA damage repair, transcription regulation, chromatin remodeling, cell cycle checkpoint control, and apoptosis	Breast cancer [19943104]
RUNX3	Hypoxia and immune cell maintenance	Hepatocellular carcinoma [26147747]
KISS1	Tumor differentiation, the depth of invasion, lymph node metastasis, and distant metastasis	Bladder cancer [25272010]
RASSF1	Proliferation, invasion, and apoptosis	Non-small-cell lung cancer [21351083]
MEG3	Proliferation	Hepatocellular carcinoma [25641194]
CDH4	Proliferation, invasion, and metastasis	Gastric cancer [26147747] [23982143]
Keap1	Oxidative stress and reductive stress	Pancreatic cancer [26497117]
KLF17	Invasion and epithelial–mesenchymal transition	Breast cancer [28744404]
SHP1	Tumor differentiation or muscular infiltration depth	Endometrial carcinoma [26597461]
CDX2	Lymph node metastasis and tumor, nodes, metastasis stage	Gastric cancer [26147747]
PPARG	Proliferation and migration and Wnt/β-catenin signaling pathway	Gastric cancer [26147747] Colorectal cancer [22286757]
FOXO4	Proliferation and metastasis	Gastric cancer [26147747]
RIP3	Cell survival, cell apoptosis, and cell necrosis	Colorectal cancer [28981102]
Slit3	Invasion and metastasis	Gastric cancer [23982143]
CDH1	Invasion and epithelial-to-mesenchymal transition	Prostate cancer [22330138] [29466696] Osteosarcoma [26548607]
IGFBP3	Colony formation, migration, and invasion	Prostate cancer [22330138] Hepatoblastoma [29507645]
GPX3	ROS, migration, invasion, metastasis	Prostate cancer [22330138]
UBE2L6	Apoptosis	Cervical cancer [29157076]
RGS2	Proliferation	Bladder cancer [25323766]
miR-145	Proliferation, migration and invasion	Non-small-cell lung cancer [25961369]

Abbreviations: UHRF1, ubiquitin-like with PHD and RING finger domains 1; TSGs, tumor suppressor genes; ROS, reactive oxygen species.

Xue et al., OncoTargets &Therapy 2019

Discovered recently

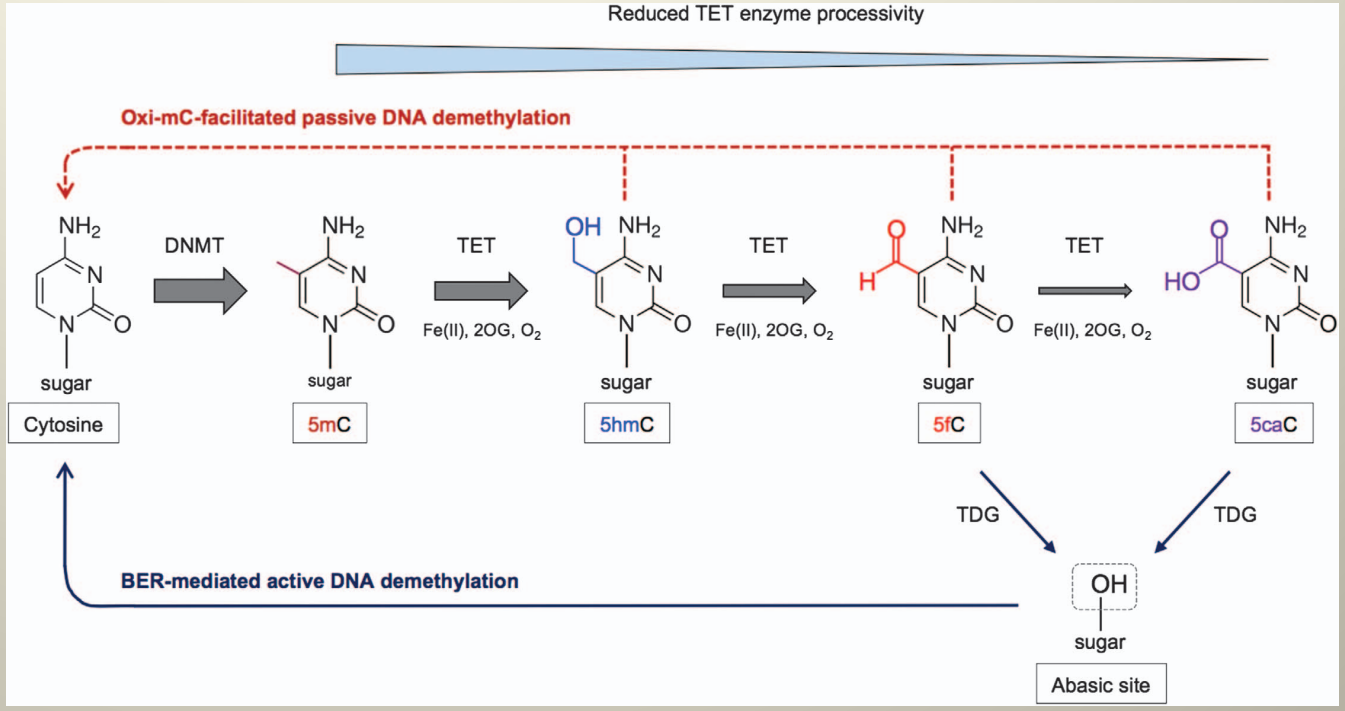
TET DNA-demethylating enzymes Three members : TET1-3

Ten-Eleven Translocation enzymes

Stepwise oxidation reactions, converting 5mC to 5-hydroxymethylcytosine (5hmC) to 5-formylcytosine (5fC), and finally to 5-carboxylcytosine (5caC)

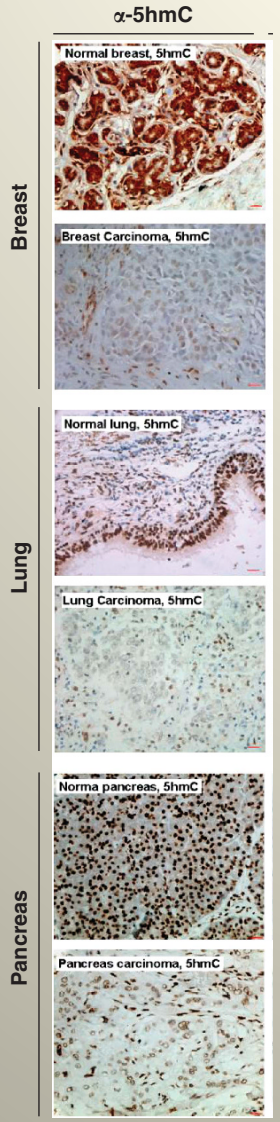
Subsequent decarboxylation of 5fC and 5caC by a thymine-DNA glycosylase (TDG) or other DNA repair enzymes, leading to DNA demethylation

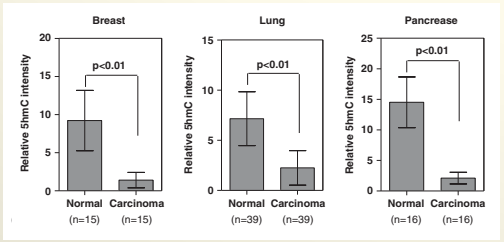
Function of TET proteins in DNA demethylation



An et al., Experimental & Molecular Medecine 2017

Disruption of normal DNA demethylation is thought to be associated with oncogenesis





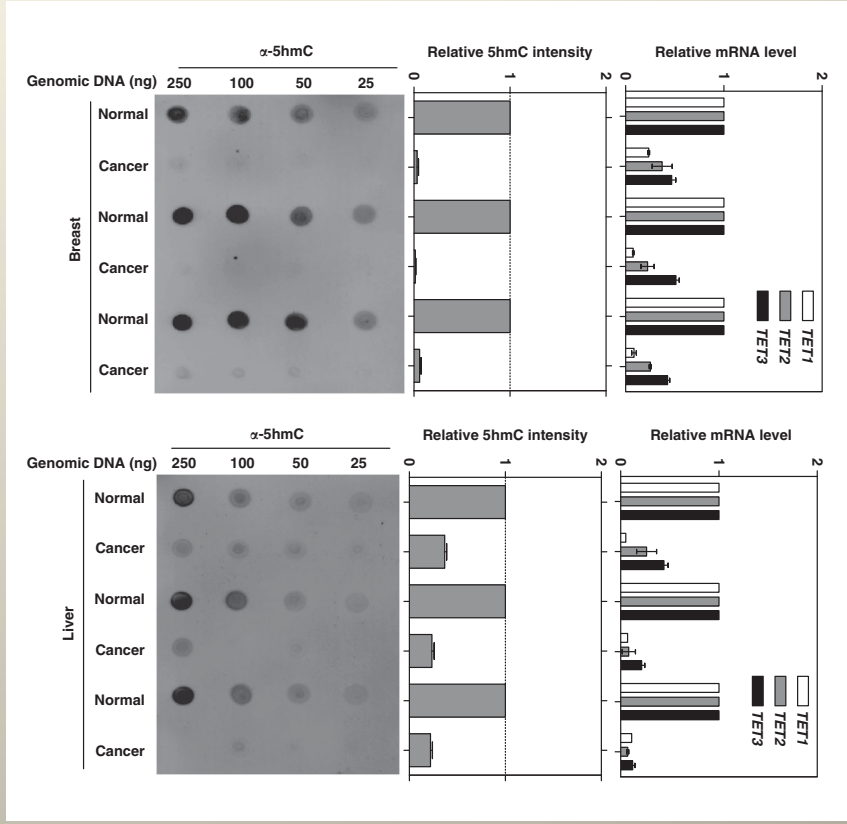
5hmC is reduced
in multiple human tumors

5hmC as a biomarker
whose decrease would tightly be associated with tumor development

Mechanism ??

Reduced 5hmC is associated with substantial reduction of TET gene expression

Quantitative dot-blot assay using genomic DNA



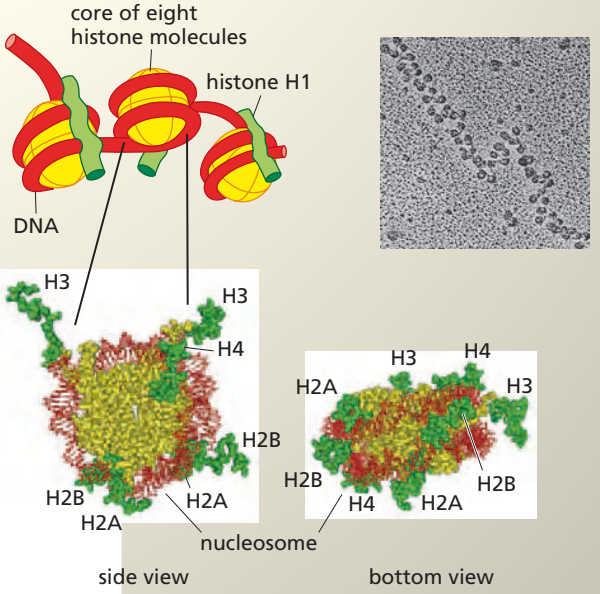
Yang et al., Oncogene 2013

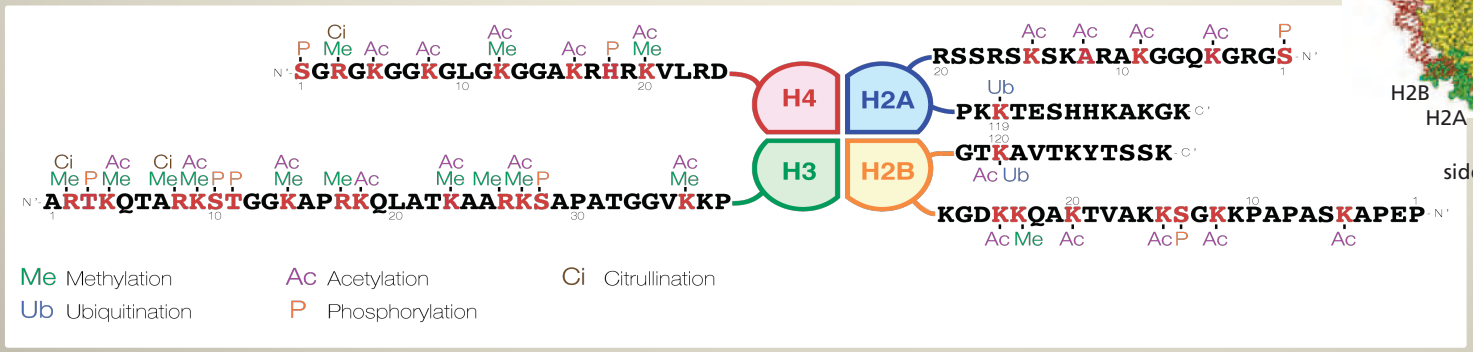
Histone modifications and Chromatin remodeling

The basic unit of the chromatin is the nucleosome

147 base pairs of DNA wrapped around an octamer of core histones

(made of two molecules of each H2A, H2B, H3 and H4 histones)



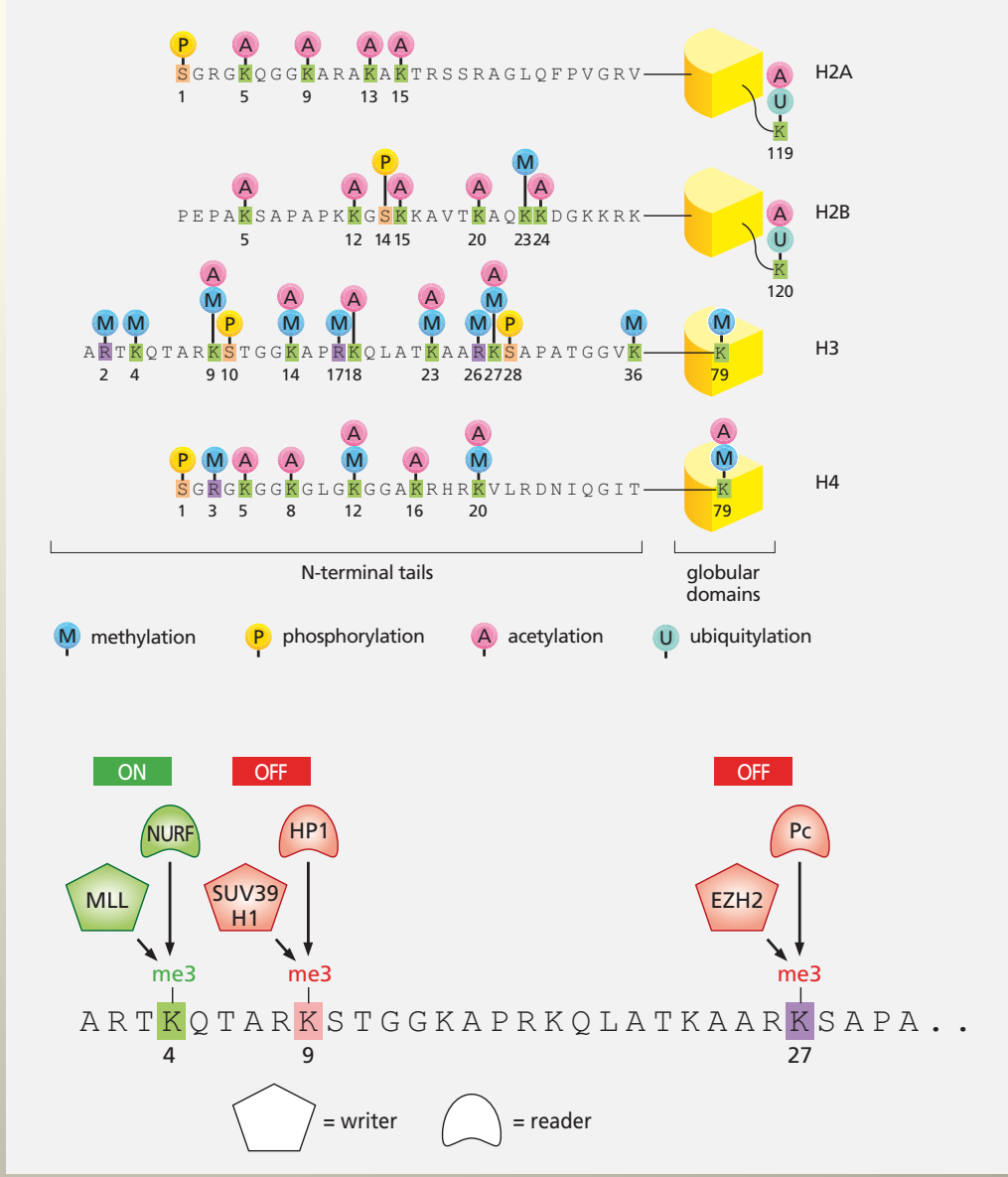


Modulation of the structure of the chromatin fiber by diverse PTMs is critical for the regulation of gene expression, since it determines the accessibility and sequential recruitment of regulatory factors to the underlying DNA

Histone modifications and Chromatin remodeling

N-terminal histone tails can be methylated acetylated, phosphorylated and ubiquitinated

*These modifications are attached by histone « **writers** », recognized by histone « **readers** », and removed by histone « **erasers** »*



Examples :

Trimethylation of H3K4 by the MLL HMT writer is recognized by a NURF reader complex

⇓

Contributes to gene activation

Trimethylation of H3K9 or K27, once read, triggers the formation of heterochromatin

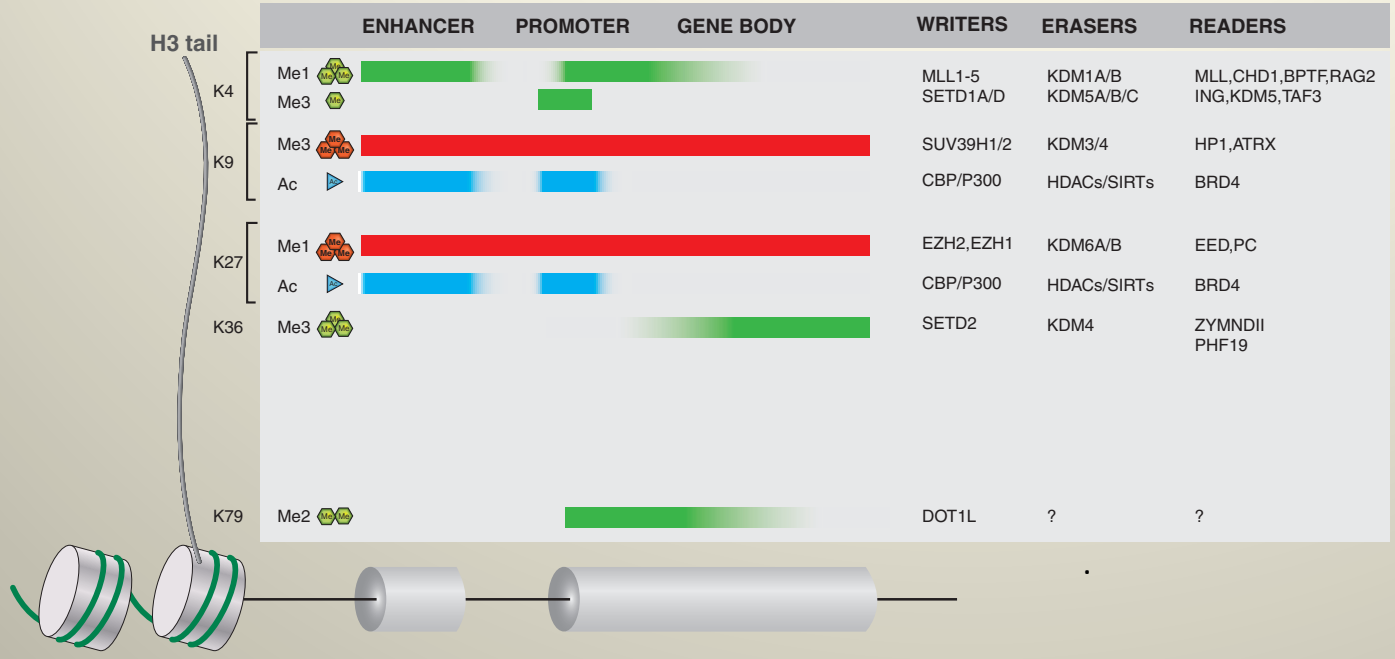
⇓

Triggers gene repression

Histone writers, readers and erasers in cancer

Among the most frequently mutated targets in cancer

Histone H3 tail lysine residues frequently subject to PTMs



Histone modifications accumulate during tumorigenesis

Genomic studies have clearly implicated dysregulation of chromatin modifiers as drivers in many types of cancer

Interplay between cancer genetics and epigenetics

Real complexity of the oncogenic process

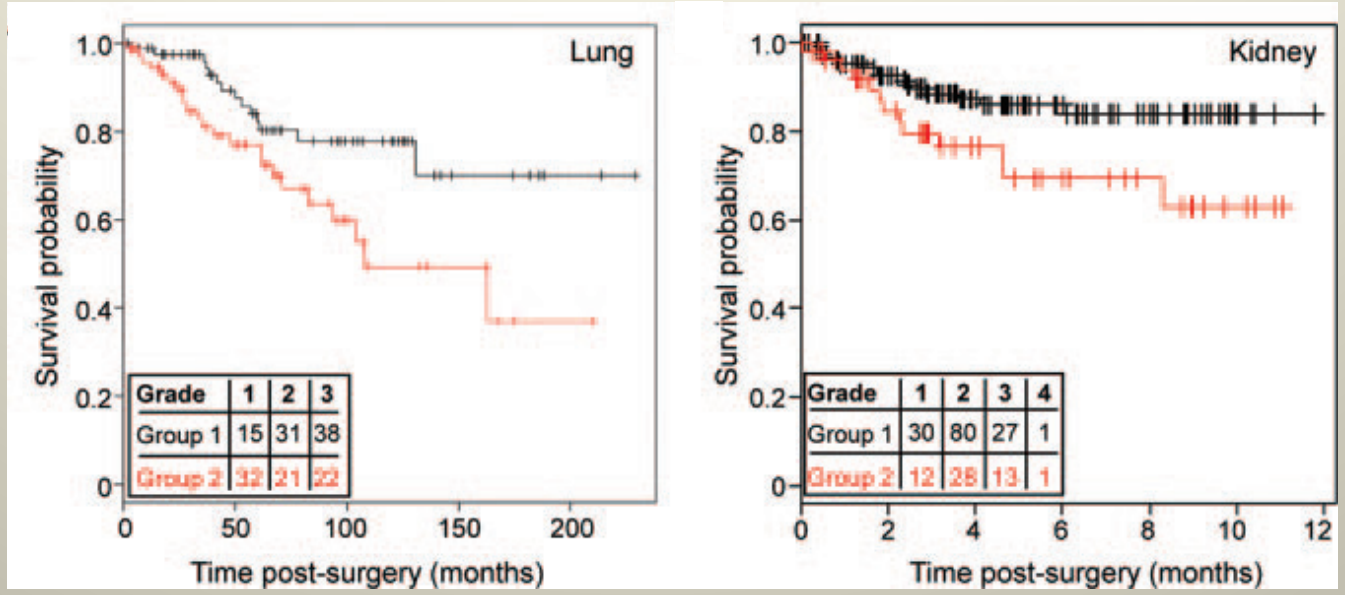
Histone modifications in cancer

Global levels of histone modifications predict prognosis in different cancers

Lower levels of H3K4me2 and H3K18ac predict poorer survival probabilities in both lung and kidney cancer patients

Patients with normal level of histone modifications

Patients with low level of histone modifications



Common prognostic epigenetic patterns of adenocarcinomas of different tissue origins

Seligson et al., Biomarkers, Genomics, Proteomics, and Gene Regulation 2019

Histone methylation THE WRITERS

Histone methylation *(lysine and arginine)* can either promote or inhibit gene expression

KMTs are highly specific enzymes, meaning that they are highly selective for lysine residues they can methylate and the specific methylation degree they can achieve

Enzymes or proteins that regulate histone methylation in cancer

Enzymes	Synonyms	Role in cancer	Cancer type	Mechanism
Histone methyltransferases (lysine): the writers for lysine				
EZH			*all types of cancer*	
EZH1	KIAA0388	Promoter	Breast cancer, prostate cancer, bladder cancer, colorectal cancer, liver cancer, gastric cancer, melanoma, lymphoma, myeloma, Ewing's sarcoma, glioblastoma, thyroid carcinoma, esophageal squamous cell carcinoma, lung cancer, ovarian cancer, renal cancer[392,450–452]	Promotes cell proliferation, colony formation, migration and tumor metastasis; is associated with cancer stem cell maintenance; predicts chemotherapeutic efficacy and response to tamoxifen therapy (E-cadherin, RUNX3, MEK-ERK1/2-Elk-1 pathway)
EZH2	KMT6, ENX-1, MGC9169			
SET2			*solid tumors*	
KMT3A	SETD2, SET2, HIF-1,	Suppressor	Renal cancer, lung cancer[453,454]	Maintains genome integrity and attenuates cisplatin resistance (ERK signaling pathway)
WHSC1	NSD2, WHS, TRX5	Promoter	Prostate cancer, gastric cancer[455,456]	Promotes cell invasive properties, EMT and cancer metastasis
WHSC1L1	NSD3, MGC126766	Promoter	Breast cancer, head and neck cancer[457]	Is associated with ERα overexpression and enhances the oncogenic activity of EGFR
Others			*leukemia*	
DOT1L	KMT4	promoter	MLL-rearranged leukemia, colorectal cancer, breast cancer, ovarian cancer[391,478,479]	Increases EMT, cancer stemness and tumorigenic potential and is required for MLL rearrangement

Cheng et al., Signal Transduction and Targeted Therapy 2019

Methyl-histone recognition proteins

Representative chromodomain-containing proteins in humans are HP1 and Chd1, which can recognize H3K9me and H3K27me, respectively

Enzymes or proteins that read histone methylation in cancer

Enzymes	Synonyms	Role in cancer	Cancer type	Mechanism
Methyl-histone recognition proteins: the readers				
Chromodomain				
HP1	/	Promoter	Breast cancer[507]	Overexpression of HP1 is associated with breast cancer progression
Chd1	/	Promoter	Prostate cancer[508]	Is associated with cell invasiveness, double-strand break repair and response to DNA-damaging therapy
		Suppressor	Prostate cancer[509]	Loss of MAP3K7 and CHD1 promotes an aggressive phenotype in prostate cancer

Cheng et al., Signal Transduction and Targeted Therapy 2019

Histone demethylases HDMs or KDMs

KDMs can be classified into two groups :

The amine-oxidase type lysine-specific demethylases (LSDs)

The highly conserved JumonjiC (JMJC) domain-containing histone demethylases

The LSD1 and KDM2 family possesses context-dependent tumor-promoting and -inhibiting functions

LSD1 (KDM1A) is one of the best-studied KDMs and has been found to be increased in multiple cancers

Enzymes or proteins that erase histone methylation in cancer

Enzymes	Synonyms	Role in cancer	Cancer type	Mechanism
KDMs: the erasers				
KDM1				
KDM1A	LSD1	Promoter	Breast cancer, lung cancer, prostate cancer, liver cancer, pancreatic cancer, gastric cancer[519–521]	Contributes to cell proliferation and stem cell maintenance and self-renewal (p21, AR, HIF1α-dependent glycolytic process)
		Suppressor	Breast cancer[522]	Inhibits invasion and metastatic potential
KDM1B	LSD2	Promoter	Breast cancer[523]	Contributes to cancer progression and cancer stem cell enrichment
KDM2/JHDM1				
KDM2A	JHDM1A, CXXC8	Promoter	Breast cancer, gastric cancer, lung cancer, cervical cancer[524–526]	Promotes cancer cell proliferation, metastasis, and invasiveness (HDAC3, TET2)
KDM2B	JHDM1B, FBXL10,	Promoter	Prostate cancer, breast cancer, gastric cancer[527,528]	Promotes cell migration, angiogenesis, and the self-renewal of cancer stem cells

Cheng et al., Signal Transduction and Targeted Therapy 2019

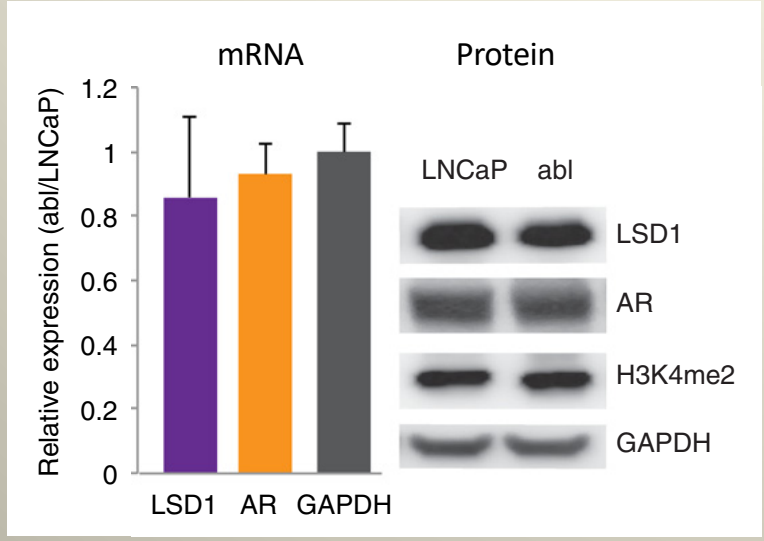
LSD1-mediated epigenetic reprogramming in CRPC activates a group of cell-cycle genes, including CENPE, to drive prostate cancer progression

Demethylation of the repressive histone mark at H3K9 results in the derepression of AR (Androgen Receptor) target genes

AR = Androgen Receptor
Key driver of prostate cancer
LSD1 = coactivator of AR transcriptional activity

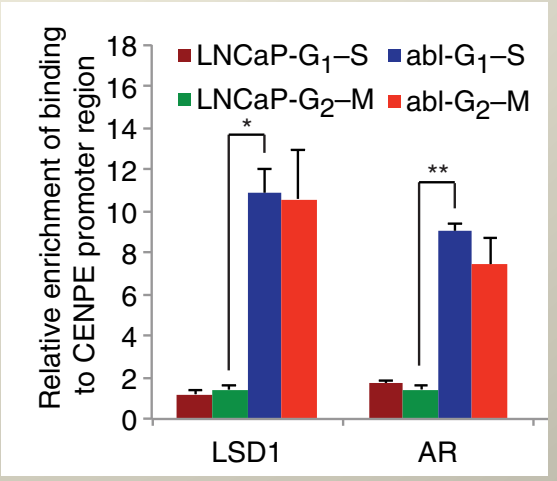
→ *Androgen deprivation therapy*
But develop castration-resistant prostate cancer (CRPC)

LNCaP, canonical androgen-dependent prostate cancer cell line
abl, androgen-independent derivative of LNCaP cells



No significant difference in LSD1 mRNA level between primary and metastatic CRPC tumors

CENPE is a crucial kinetochore-associated kinesin motor protein with an essential role in metaphase chromosome alignment and satisfaction of the mitotic checkpoint



CENPE has much stronger LSD1 binding in its promoter in abl cells compared with LNCaP cells
➡ Induction of its expression

There is a reprogramming of LSD1 binding

Liang et al., Cancer Research 2017

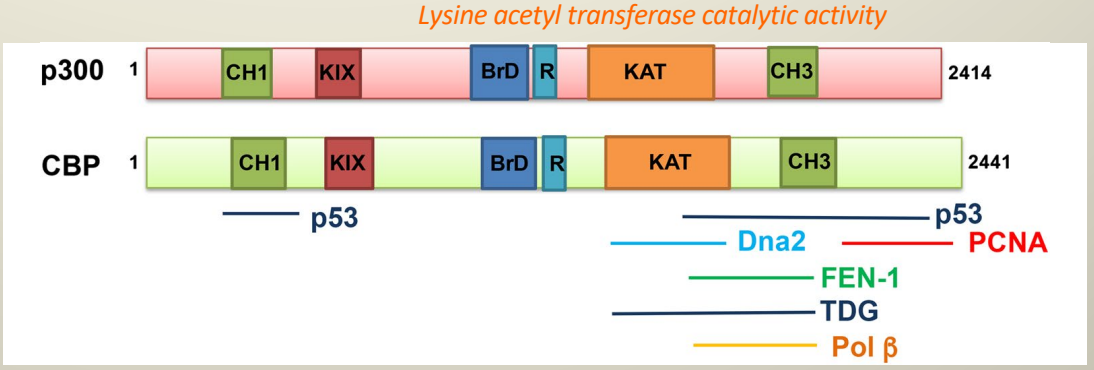
Histone acetylation THE WRITERS

The enzymes that catalyze the addition of acetyl groups to histone lysine residues are the lysine (K) acetyltransferases (**KATs**), commonly referred to as histone acetyltransferases (**HATs**)

The addition of an acetyl group can occur at multiple lysine residues on histone tails

Three major families :

- ✓ the Gcn5-related N-acetyltransferase family (GNAT)
- ✓ the MYST family (MOZ, Ybf2, Sas2, TIP60)
- ✓ the orphan family (CBP/EP300 and nuclear receptors)



Dutto et al., 2017

Influence the compaction state of chromatin by neutralizing the basic charge at unmodified lysine residues weakening the electrostatic interaction between negatively charged DNA and histones

Genetic or epigenetic aberrations affecting HAT expression, stability, or domain function can have chromatin regulatory consequences

Audia and Campbell, Cold Spring Harb Perspect Biol 2016

Acetyltransferases in cancer

Appropriate acetylation within cells is important since upregulation or downregulation of HATs is associated with tumorigenesis or poor prognosis

Altered acetylation of H4K16 has been linked to various cancers

Loss of p300 has also been associated with hematological malignancies. Therefore, both CBP and p300 seem to function as tumor suppressors

During cancer development, the expression of HAT genes can be disrupted by chromosomal translocations

MLL-CBP, and MLL-p300 (MLL, mixed lineage leukemia) have been identified in hematological malignancies

Missense point mutations in p300 are found in colorectal adenocarcinoma, gastric adenocarcinoma and breast cancer

Cheng et al., Signal Transduction and Targeted Therapy 2019

Acetyl-lysine recognition proteins

The BET (bromodomain and extraterminal domain) protein family

Four members : BRD2, BRD3, BRD4, and BRDt

The bromodomain (BRD) motif contains a hydrophobic pocket to identify acetyl-lysine of histones

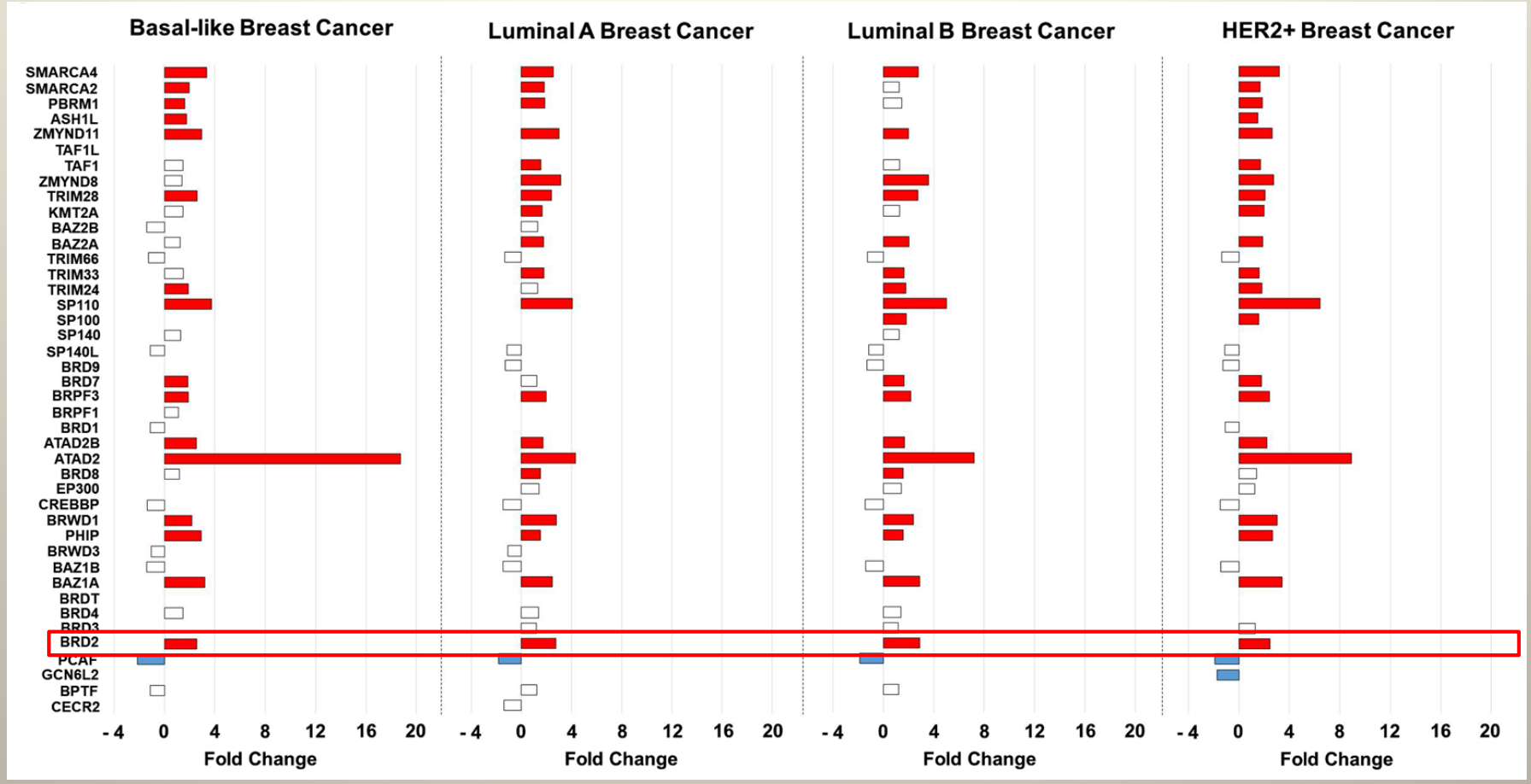
The specificity of different BRDs depends on the sequences within the loops that form the hydrophobic pocket. Therefore, each BRD has a preference for different histones

BET proteins are potential therapeutic targets in various cancers, including nuclear protein in testis (NUT)-midline carcinoma, multiple myeloma, lymphoma, lung cancer, and neuroblastoma

The BET proteins in cancer

BRD domain-containing proteins

Overexpression of BRD2 in breast cancer



Fold change gene expression compared with normal breast tissue

Perez-Pena et al., Scientific Reports 2019

The BET proteins in cancer

NUT (NUclear protein of the Testis) midline carcinoma (NMC) is an aggressive type of squamous cell carcinoma that is defined by the presence of *BRD-NUT* fusion oncogenes

BRD4-NUT chimeric proteins binds the promoter region of Myc, a powerful oncoprotein in high-grade cancers, and drives tumor growth by blocking differentiation

BRD4-NUT binds chromatin through the dual bromodomains of BRD4,
and the NUT moiety recruits p300 to chromatin forming megadomains enriched in histone marks that are associated with active transcription, driving the expression of associated genes, including MYC

Dysregulation of MYC by BRD-NUT fusion proteins has a central role in the pathogenesis of NMC

NMC can be seen as an epigenetic disease

Grayson et al., Oncogene 2014
Morrison-Smith et al., Mol. Cancer Therapeutics 2020

Histone acetylation THE ERASERS

Histone deacetylases HDACs, 18 in the human genome

Four classes :

- ✓ Class I, transcriptional corepressors with the deacetylase domain at the N-terminus and diversified C-terminal regions (HDAC1, HDAC2, HDAC3, and HDAC8)
- ✓ Class II, with the deacetylase domain at a C-terminal position (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10)
- ✓ Class III, HDACs are yeast silent information regulator 2 (Sir2)-like proteins (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7)
- ✓ Class IV, involves one protein (HDAC11)

As for HATs, their substrates are also not limited to histones

More than 3600 acetylation sites on 1750 proteins have been identified, including the tumor suppressor p53 and the cytoskeletal protein α-tubulin

HDACs are also capable of regulating gene transcription by deacetylating other proteins that are responsible for epigenetic events, such as DNMTs, HATs and HDACs

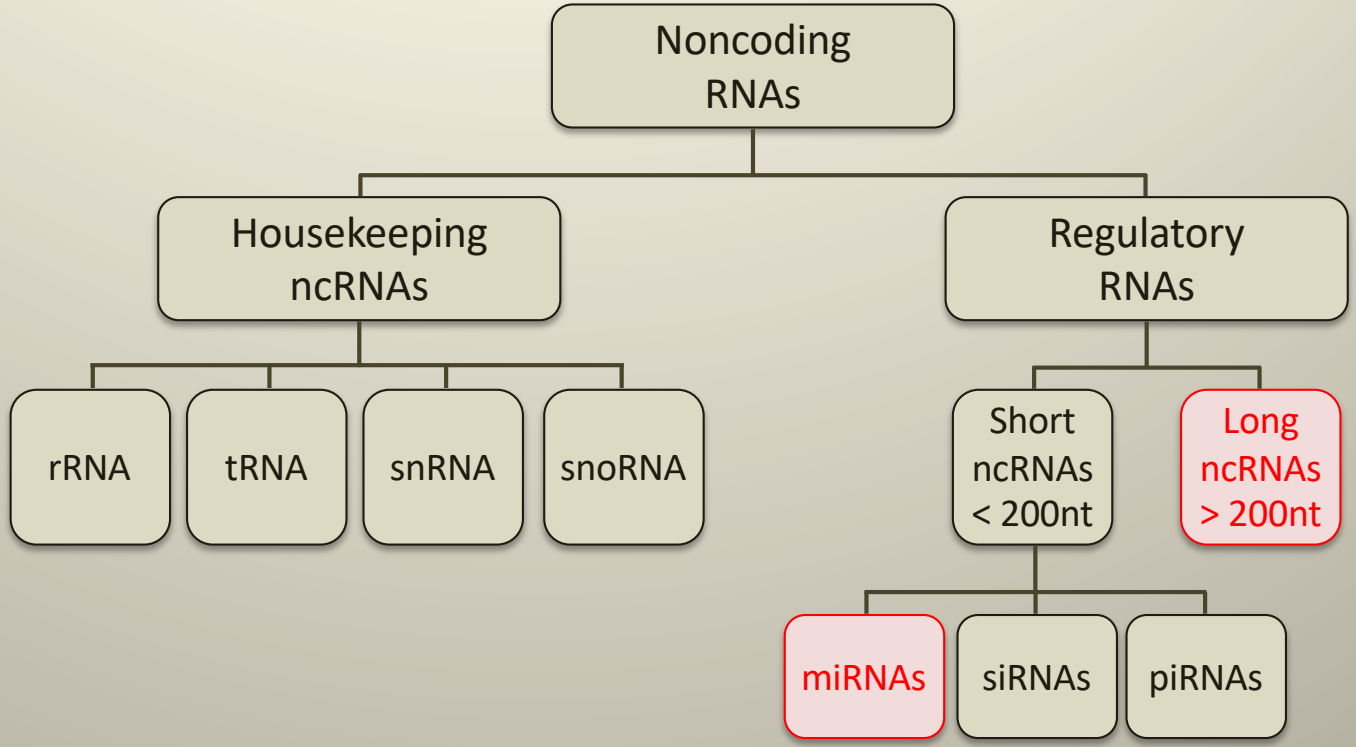
→ **Alterations in HDACs in cancers usually result in aberrant deacetylation and inactivation of tumor suppressor genes**

Cheng et al., Signal Transduction and Targeted Therapy 2019

Noncoding RNAs (ncRNAs)

Different types of ncRNAs can be distinguished :

- ✓ microRNAs (miRNAs) *small RNAs between 19 and 22 nucleotides in length*
- ✓ small interfering RNAs (siRNAs)
- ✓ piwi-interacting RNAs (piRNAs)
- ✓ long noncoding RNAs (lncRNAs)



miRNAs in tumorigenesis

- ✓ Target more than 50% of the genome
- ✓ Are key epigenetic actors
- ✓ Their altered expression have been identified in all types of human cancers
- ✓ Tumor-promoting and tumor-suppressing miRNAs
- ✓ Tissue specific expression : molecular signature
- ✓ Predictive markers that could be used in personal therapy

miRNA	Roles in gastrointestinal cancers	Target genes
Potential tumor suppressor miRNAs		
miR-15b, miR-16	miR-15b and miR-16 play a role in the development of MDR in gastric cancer cells by modulation of apoptosis via targeting BCL2	BCL2
miR-34a	mrR-34a functions as a tumor suppressor and induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells	E2F pathway
miR-143, miR-145	miR-143 and miR-145 are downregulated in colorectal cancer	ERK5
Potential oncogenic miRNAs		
miR-17-92 cluster	miR-17-92 cluster is overexpressed in various human malignancies, including colon cancer	E2F1 (miR-17-5p, miR-20a) TGFBR2 (miR-20a)
miR-21	miR-21 is upregulated in various human malignancies including cholangiocarcinoma, and gastric and colon cancers	PTEN
miR-106a	miR-106a is upregulated in colon cancer	RB-1
miR-106b-25 cluster	miR-106b-25 cluster, which is upregulated in human gastric cancers and activated by E2F1, impairs the TGF-β tumor suppressor pathway	p21 Bim E2F1
miR-155	miR-155 is overexpressed in various human malignancies, including B-cell lymphoma and colon cancer	TP531NP1

Long noncoding RNAs (lncRNAs)

Their role in cancer development is only beginning to be uncovered

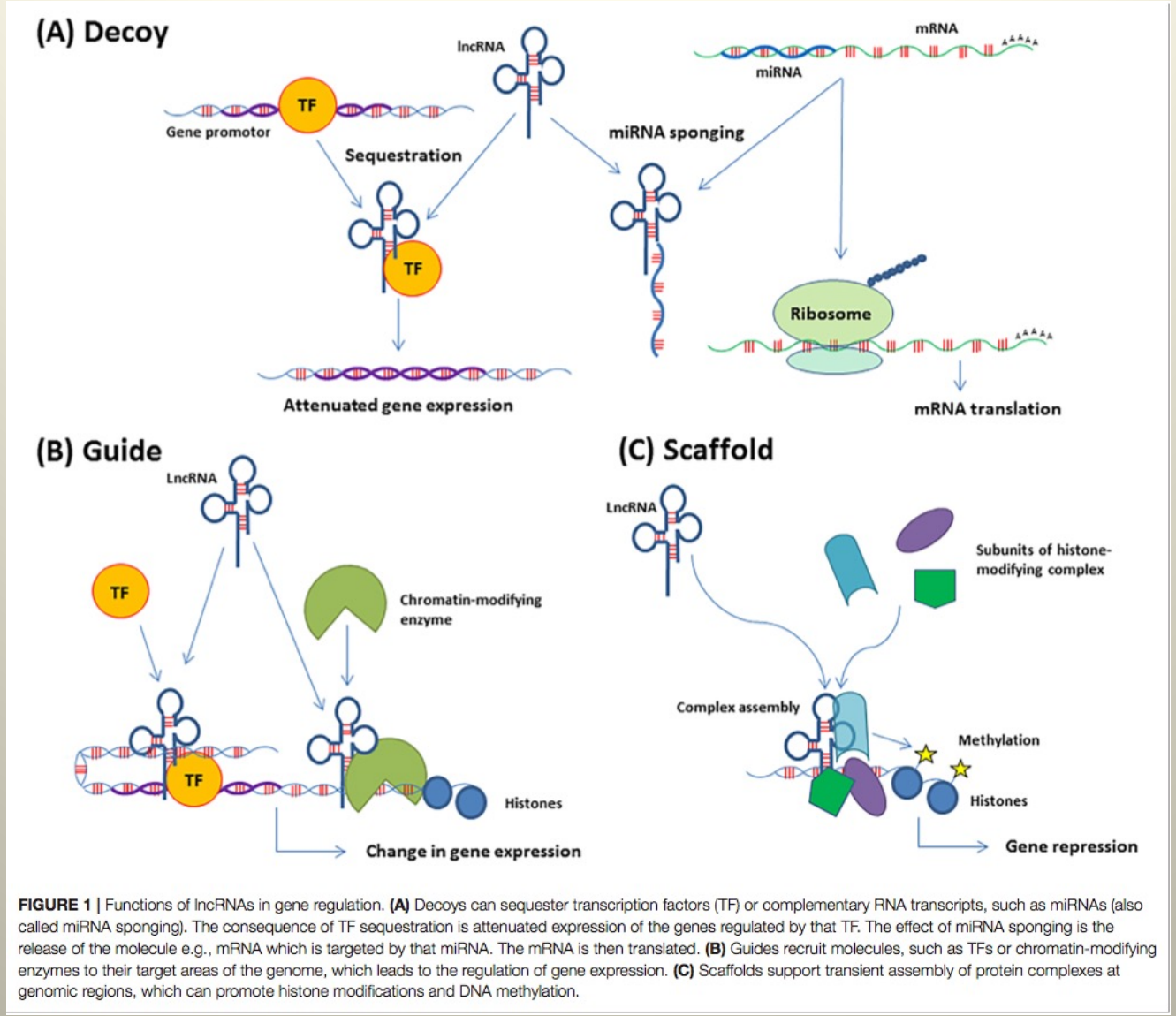


FIGURE 1 | Functions of lncRNAs in gene regulation. **(A)** Decoys can sequester transcription factors (TF) or complementary RNA transcripts, such as miRNAs (also called miRNA sponging). The consequence of TF sequestration is attenuated expression of the genes regulated by that TF. The effect of miRNA sponging is the release of the molecule e.g., mRNA which is targeted by that miRNA. The mRNA is then translated. **(B)** Guides recruit molecules, such as TFs or chromatin-modifying enzymes to their target areas of the genome, which leads to the regulation of gene expression. **(C)** Scaffolds support transient assembly of protein complexes at genomic regions, which can promote histone modifications and DNA methylation.

Abildgaard et al., Front. Oncol. (2020)

LncRNAs in tumorigenesis

Table 1 Biological function of lncRNAs in carcinomas.

Biological Function	LncRNA	Target Gene/Pathway	Cancer Type	Reference
Promote proliferation, migration, and invasion	LINC00052	miR-608/EGFR	Head and neck cancer	32
	AC009022.1	miR-497-5p	Colorectal cancer	33
	DLGAP1-AS1	miR-486-5p	Hepatocellular cancer	34
	GHSROS	—	Breast cancer	35
	LINC00337	TIMP2/DNMT1	Non-small-cell lung cancer	36
	AK001058	ADAMTS12	Colorectal cancer	37
	FOXD2-AS1	miR-185-5p	Thyroid cancer	38
	LINC00460	—	Colorectal cancer	39
	LINC00908	Sox-4	Hepatocellular cancer	40
	PVT1	Smad3/miR-140-5p	Cervical cancer	41
	RAIN	RUNX2	Breast and thyroid cancer	42
	LINC00673	miR-515-5p/MARK4/Hippo	Breast cancer	43
	TTN-AS1	KLF15	Colorectal cancer	44
	SNHG4	ZIC5	Prostate cancer	45
	SOX2-OT	miR-369-3p/CFL2	Prostate cancer	46
	LINC01559	YAP	Pancreatic cancer	47
	VCAN-AS1	p53	Gastric cancer	48
Suppress proliferation and invasion	OSER1-AS1	miR-372-3p/Rab23	Hepatocellular cancer	49
	ZEB1-AS1	ZEB1	Esophageal cancer	50
	NBAT-1	PKM2	Esophageal cancer	51
	ENST00000489676	MiR-922	Thyroid cancer	52
	CASC2c	ERK1/2, Wnt/β-catenin	Hepatocellular cancer	53
	GAS5	YAP	Colorectal cancer	54
	ADAMTS9-AS2	CDH3	Esophageal cancer	55
	TCONS_00020456	Smad2/PKCα	Glioblastoma	56
Estimate prognosis and efficacy	UCA1, H19	5-fluorouracil	Rectal cancer	57
	ADAMTS9-AS2	FUS/MDM2	Glioblastoma	58
	INCAC112721.1, AL356479.1, LINC00466	hsa-miR-204	Breast cancer	59
	GAS5, HOTAIR, H19, MALAT	—	Colorectal cancer	60
	HOXA-AS3	HOXA3	Non-small-cell lung cancer	61
Act as potential biomarkers	MALAT1	—	Breast cancer	62
	HOTAIR	—	Breast cancer	63
	PURPL, NONHSAT062994	—	Gastric cancer	47
	SNHG11	—	Colorectal cancer	64
	SNHG12	—	Pan-cancer	65

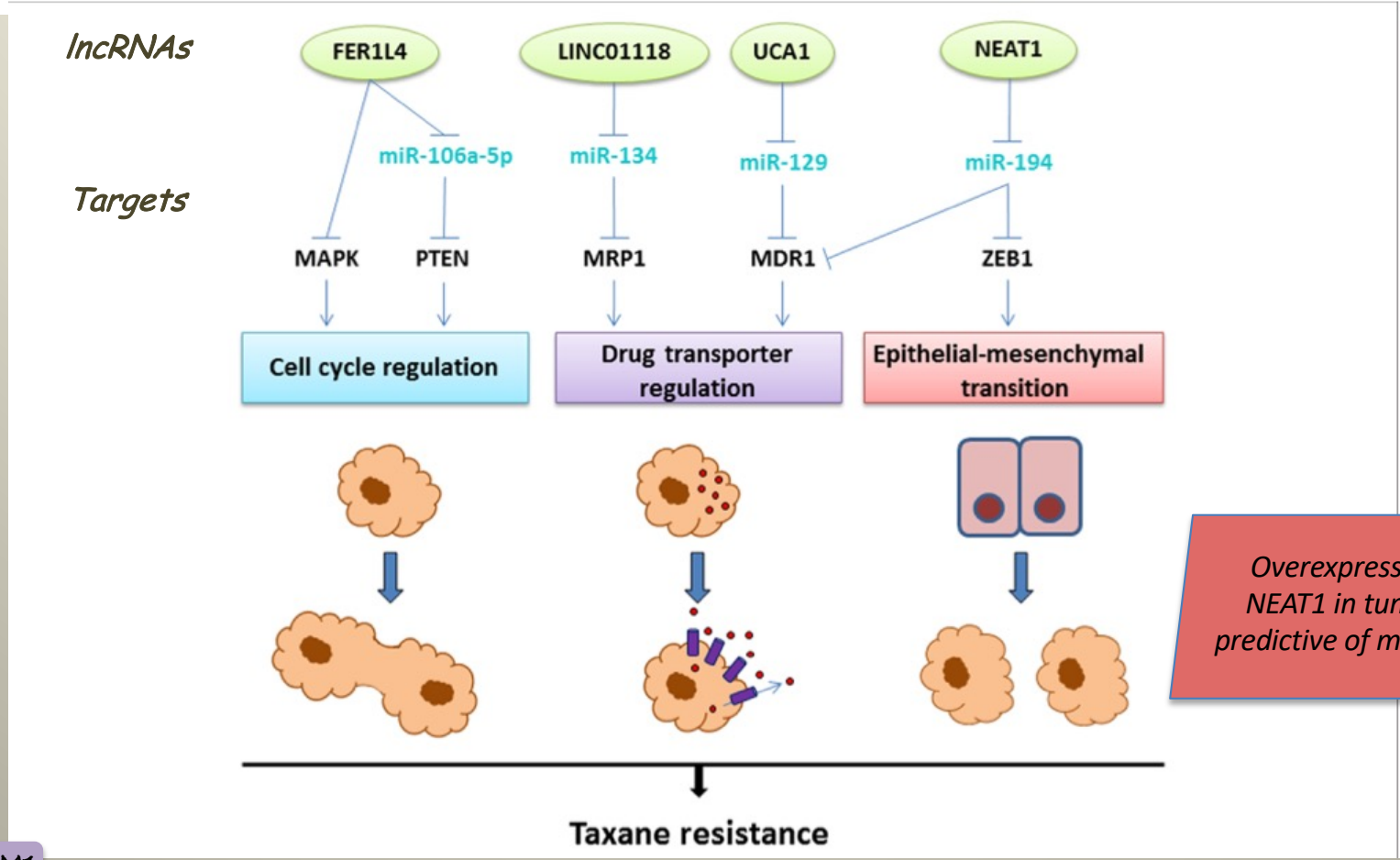
Note: References 32—48 discuss the promotion of cancer cell proliferation and invasion, references 49—56 discuss the suppression of cancer cell proliferation and invasion, references 57—61 discuss the estimation of the prognosis, and references 62—66 discuss efficacy or potential biomarkers.

Wang et al., Genes & Diseases, 2020

LncRNAs in tumorigenesis

Meta-analysis including 1333 ovarian cancer patients

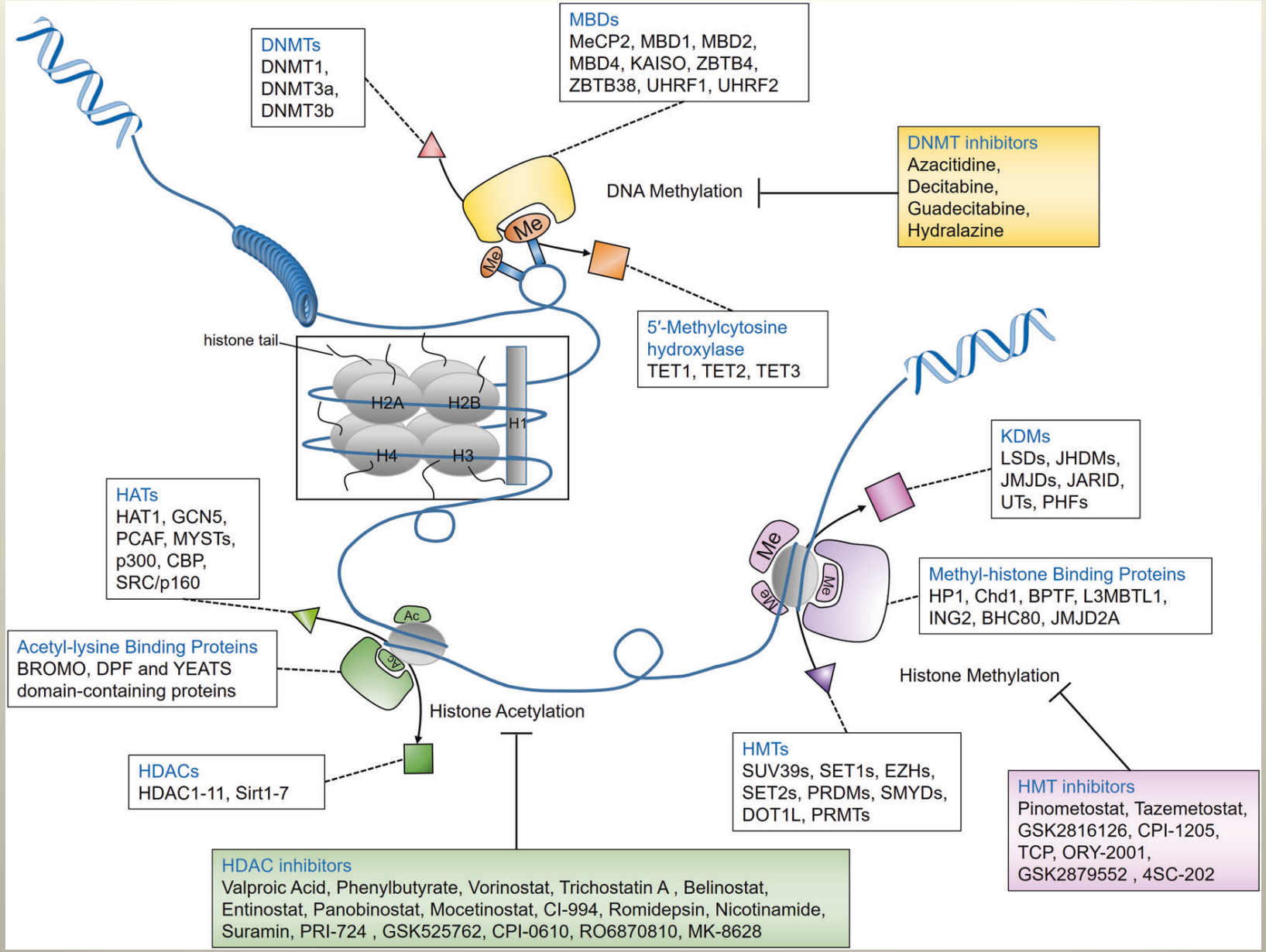
lncRNA	Category	Expression in OC tissue*	Expression in paclitaxel-resistant cell lines**	Mechanisms of resistance***
UCA1	Intergenic	N/A	↑	↓ miR-129 → ↑ abcb1
FER1L4	Pseudogene	↓	↓	MAPK
LINC01118	Intergenic	↑	↑	↓ miR-134 → ↑ abcc1
NEAT1	Intergenic	↑ (paclitaxel resistance)	↑	↓ miR-194 → ↑ ZEB1



Overexpression of NEAT1 in tumors is predictive of metastasis

Abildgaard et al., Front. Oncol. 2020

Development of epigenetic drugs



Cheng et al., Signal Transduction and Targeted Therapy 2019

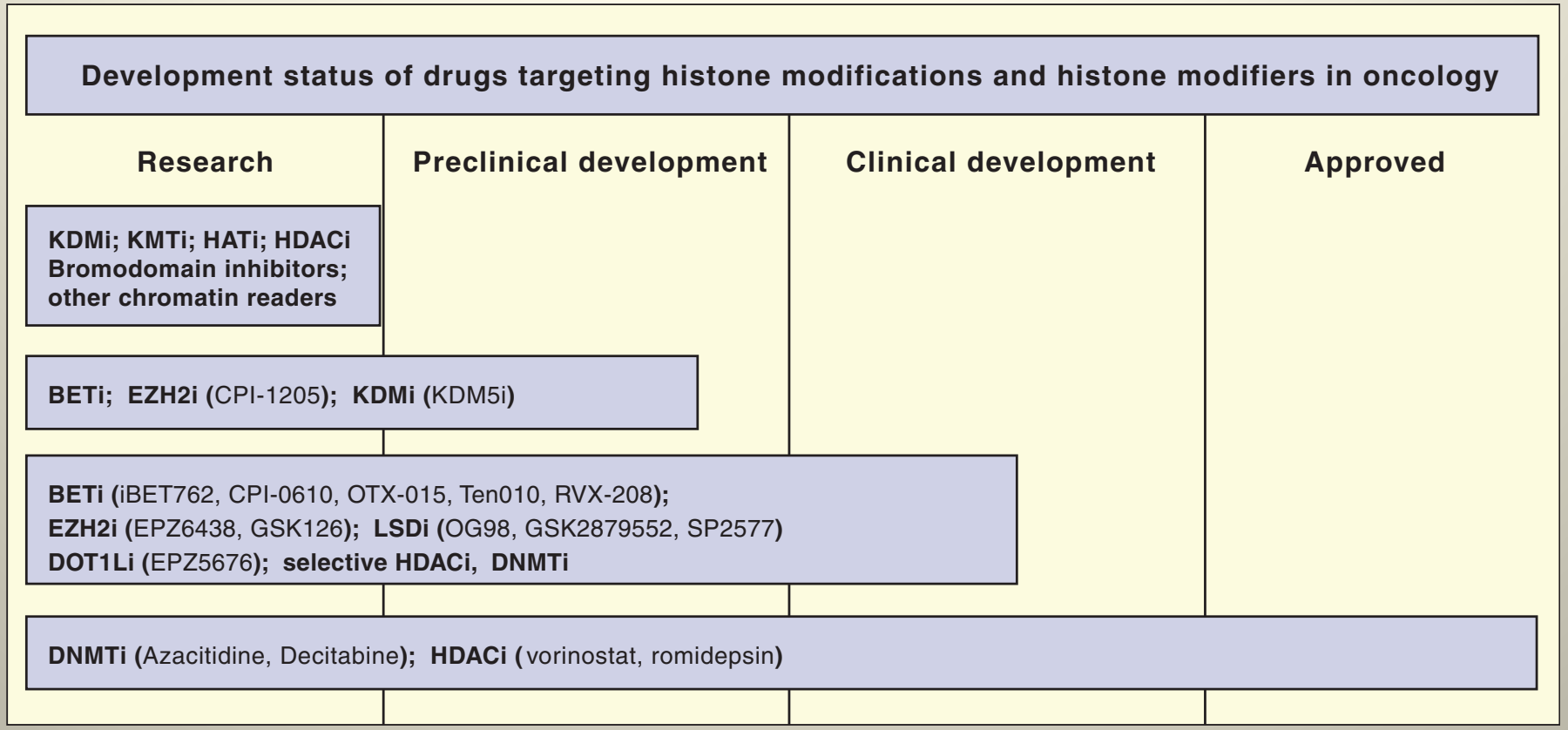
Development of epigenetic drugs

Examples of inhibitors for chromatin-related proteins

Mode of action	Target	Compound name	Types of cancer
Enzymatic inhibition	DOT1L	EPZ-5676	MLL-rearranged leukemia
	EZH2	EPZ6438, GSK126, CPI-1205	Lymphoma, malignant rhabdoid tumor
	p300	C646, A-485	hematological malignancies and androgen receptor-positive prostate cancer
	HDACs	Vorinostat, romidepsin	CTCL
PPI disruption	CARM1	EZM2302	Multiple myeloma
	Menin-MLL	MI-503, MI-463, M-525	MLL-rearranged leukemia
	WDR5-MLL	OICR-9429	C/EBPα N-terminal leukemia
	LEDGF-MLL	CP65	MLL-rearranged leukemia
Competitive binding	BET family of BRD proteins	JQ1, I-BET, I-BET151	NUT midline carcinoma, MLL-rearranged leukemia
Protein degradation	BRD4	dBET1, dBET6, ARV-825, ARV-771, BETd-246	AML, T-ALL, Burkitt's lymphoma, castration-resistant prostate cancer, TNBC

Zhao and Shilatifard, Genome Biology 2019

Development of epigenetic drugs



Audia and Campbell, Cold Spring Harb Perspect Biol 2016

Thank You