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, 2021



**UNIVERSITY OF THESSALY
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE**



**POSTGRADUATE MASTER PROGRAM
“HUMAN GENETICS –GENETIC COUNSELING”**

MASTER’S THESIS

«EPIGENETIC DRUGS AND CANCER»

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MEDICAL LABORATORY TECHNICIAN

THREE MEMBERSHIP COMMITTEE

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LARISSA, 2021



μ DNA, μ μ .
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 μ . μ μ
 μ , DNA ,
 μ . μ μ μ
 DNA, μ μ
 μ , μ RNAs.
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 μ μ μ .
 - : , , DNA, ncRNAs,
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ABSTRACT

Epigenetics involve the alterations that happen in the genome. These alterations are independent from the DNA sequence, there are dynamic, heritable and reversible. The epigenetic mechanisms are supported from the interactions of many enzymes, proteins and DNA or histones, to which DNA is wrapped. The epigenetic modifications include DNA methylation, histone modifications with the most important to be acetylation and methylation, as well as noncoding RNAs. Abnormal epigenetic alterations can lead to changes in gene expression and promote oncogenesis, via disrupting of oncogenes and tumor-suppressor genes. Moreover, mutations on epigenetic regulators can perturb their role. Epigenetic modifications are vulnerable to environments stimuli and there are reversible. For those reasons there are molecules of high significance for the use as biomarkers and as therapeutic targets for anticancer therapy. The development of epi-drugs was started many decades ago and nowadays many of them are implicated on clinical trials or have already been approved by FDA for the treatment of plenty of hematological malignancies but also for solid tumors. The use of epi-drugs can be as monotherapy or as polytherapy with other epi-drugs, chemotherapy, or radiotherapy. The combination use can enhance the effectiveness but also can ameliorate the unwanted effects that each single category of drugs can develop as monotherapy.

Keywords: epigenetic, cancer, modifications of DNA and histones, ncRNAs, epigenetic drugs

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1. μ μ μ μ μ .
μ , μ μ μ μ
, , , , μ μ
, μ μ , μ μ μ μ
..... 12

2. μ μ μ μ μ
: μ DNA, μ - RNAs 13

3. : writers, readers erasers. 14

4. μ μ 16

5. μ (DNMTs). 5-μ - DNA μ -
S- μ 5' μ μ μ μ
..... 20

6. HATs μ HDACs.
μ .
μ μ
..... 28

7. μ μ μ
. μ , μ 43

8. μ μ μ μ μ μ μ μ
DNA μ μ μ μ μ μ
..... 58

1. μ μ μ 33

2. 35

3. μ RNA μ 37

4. μ μ μ μ DNA
μ 47

5. μ μ μ μ
μ 50

6.	μ	μ	μ	μ	-	RNAs	59
	μ							

AGO	Argonaute
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BC	Breast cancer
BET	bromo- and extra-terminal
BLBCL	Diffuse large B-cell lymphoma
BRDs	Bromodomains
CD	Cytidine deaminase
CLL	Chronic lymphocytic leukemia
CRC	Colorectal cancer
CTCL	Cutaneous T-cell lymphoma
DNMTIs	Inhibition of DNMTs
DNMTs	DNA methyltransferases
EATL-II	Enteropathy-associated T cell lymphoma
EPICUP	Epigenetic diagnostic test cancer unknown prognosis
ESCs	Embryonic stem cells
ESSC	Supraglottic squamous cell cancer
EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit
FL	Follicular lymphoma
GC	Gastric cancer
HATs	Histone lysine acetyltransferases
HCC	Hepatocellular carcinoma
HDACs	Histone deacetyltransferases
HDMs	Histone demethylases
HOTAIR	Hox transcript antisense intergenic RNA
HSCs	Hematopoietic stem cells
IDH1/2	Isocitrate dehydrogenase 1 and 2
LAC	Lung adenocarcinoma
lncRNAs	Long non-coding RNAs
MBPs	DNA methyl-binding proteins
MDS	Myelodysplastic syndrome
MLD	Manual lymphatic drainage
MM	Multiple Myeloma
MPN	Myeloproliferative neoplasm
ncRNAs	non coding RNAs
NSCLC	Non-small cell lung cancer
PGCs	Primordial germ cells
piRNAs	PIWI-interacting RNAs
PRC2	Polycomb repressive complex 2
PTCL	Peripheral T-cell lymphoma
snoRNA	small nucleolar RNA
TET	Ten-eleven translocation

1.

μ μ

« » μ , « μ »

μ ,

μ .

μ , DNA,

μ .

μ , μ

μ

μ , μ

μ , μ

μ

μ , μ

μ

μ

μ DNA (Goldberg et al., 2007).

μ μ μ

/ μ , μ μ

μ ,

μ DNA μ μ ,

μ μ -μ

(Alabert et al., 2015, Budhavarapu et al., 2013).

μ μ μ (primordial germ cells, PGCs), μ μ

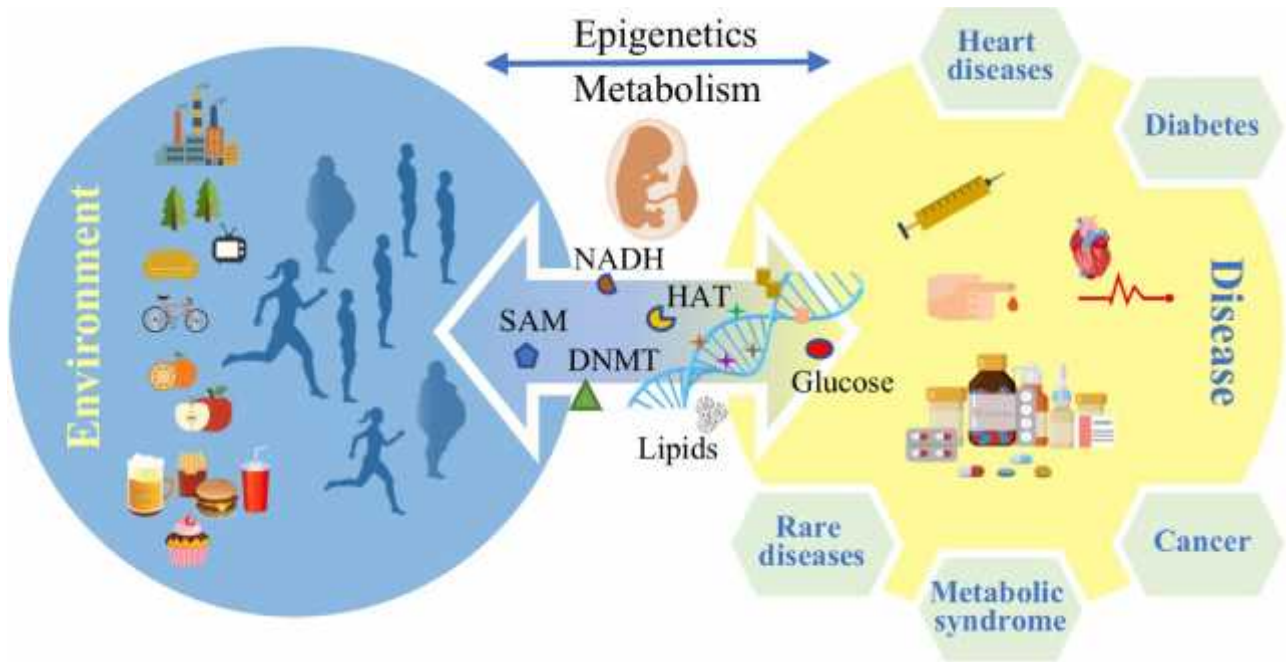
μ μ

μ (Feil and Fraga, 2012).

μ μ

μ .

μ . , μ μ , μ
 μ μ - -
 μ . , ,
 μ
 μ μ μ μ μ
 μ μ (Tzika et al., 2018).



1. μ μ μ μ μ .
 μ , μ μ μ μ
 , , μ μ
 μ , μ μ μ , μ
 μ

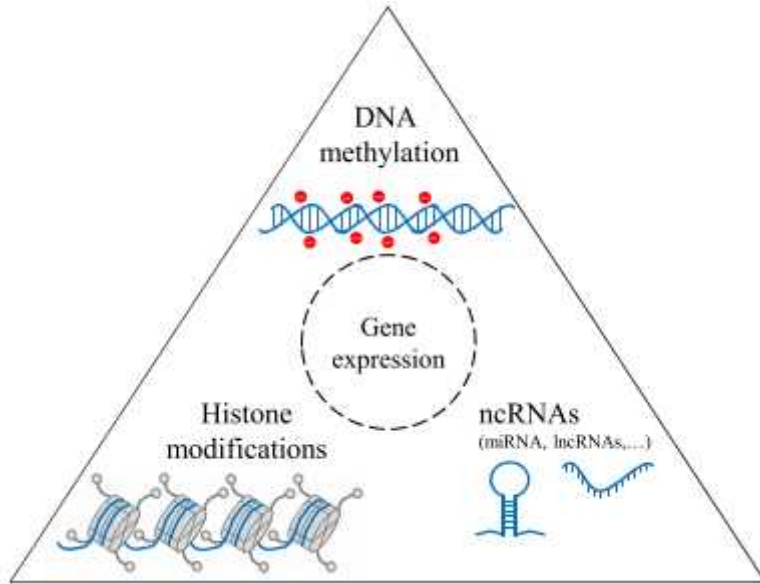
: Tzika et al., 2018.

μ , μ DNA, μ -μ
 μ - μ RNA (non coding
 RNAs, ncRNAs) (2) (Roberti et al., 2019). μ
 μ ,
 (Gibney and Nolan, 2010).

μ μ

X μ μ , μ , μ
 Homeobox μ μ

μ . (Kiefer, 2007).

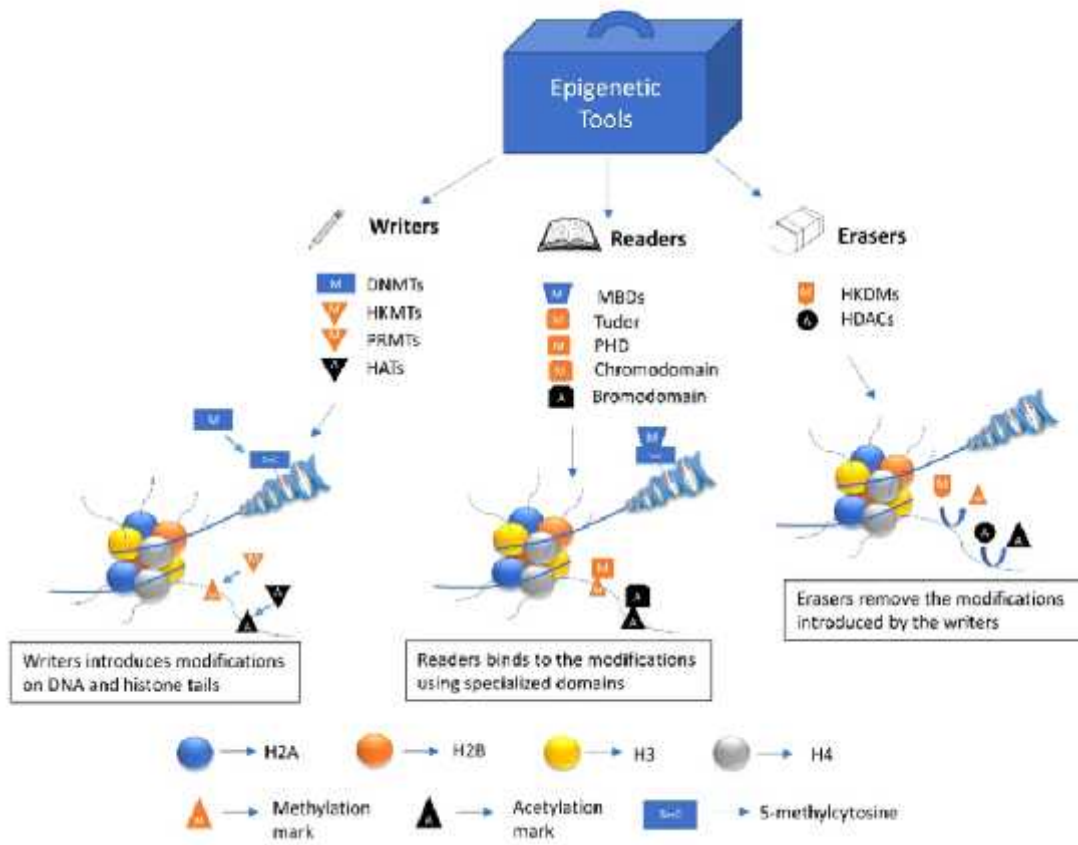


2. : μ μ DNA, μ - μ

RNAs

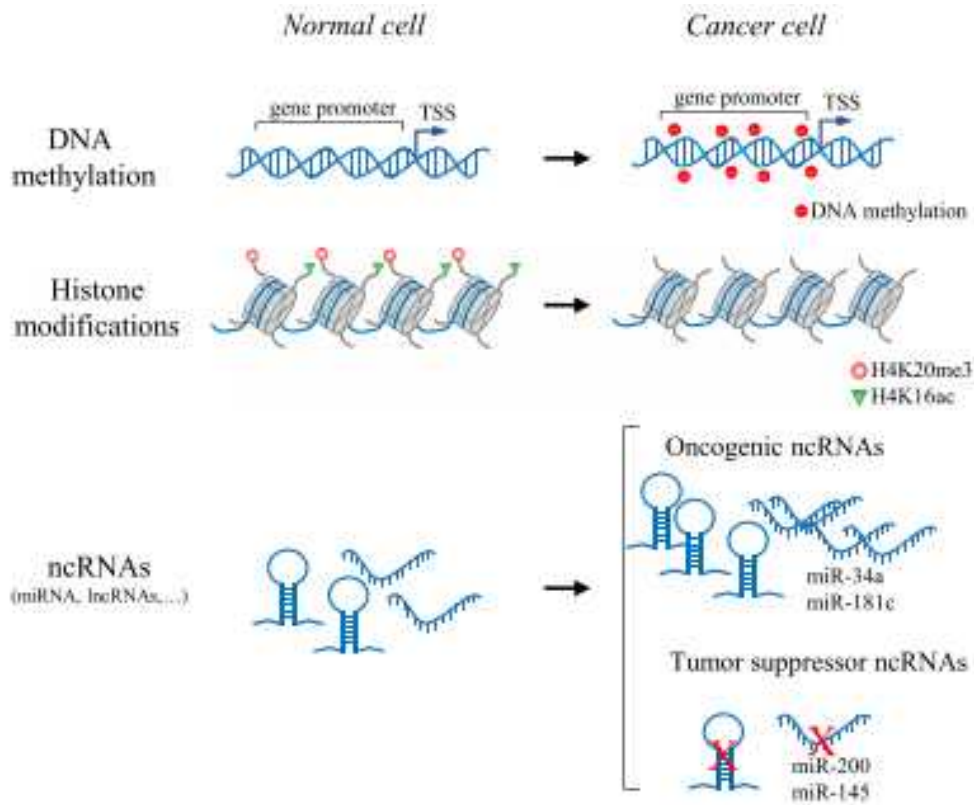
: Roberti et al., 2019

μ μ μ μ μ (writers),
 μ (erasers)
 μ μ μ μ μ (readers). , μ μ μ μ μ movers (Yan et al., 2016) (3).
 μ writers μ DNA μ ,
 μ , μ readers μ
 DNA μ
 μ μ CpG (MBPs), readers μ
 . erasers μ μ
 μ μ DNA ,
 (Biswas and Rao, 2018) (3).



3. μ : writers, readers erasers.
 μ DNA

Πηγή: (Biswas and Rao, 2018)



4. μ μ

: Roberti et al., 2019

μ μ DNA μ μ ,

μ « » (epigenetic signatures), μ

μ μ μ ,

(Hao et al., 2017, Rodríguez-Rodero et al., 2013, Fernandez et al., 2012).

μ , μ

μ μ - μ , ,

(Moran et al., 2016, Carmona et al., 2013, Heyn and Esteller, 2012).

(epigenetic diagnostic test cancer unknown prognosis, EPICUP)

μ μ , μ μ

μ DNA, μ

.
 μ
 μ , μ μ μ .
 μ μ EPICUP
 μ μ μ 38
 85 μ (Moran et al., 2016, Fernandez
 et al., 2012).
 ,
 μ μ μ ,
 μ (Kanwal and Gupta, 2012,
 Fraga et al., 2005). μ μ μ
 ,
 . ,
 , μ
 μ μ μ μ (Ozda et al., 2006).
 , μ μ μ
 , μ μ μ .
 , μ μ μ μ
 μ μ μ
 μ μ .

3.

3.1. DNA

μ DNA
μ μ μ ,
μ . μ
, μ μ ,
μ μ , μ μ
, μ ,
μ (Bernstein et al., 2007, Smith and Meissner,
2013). μ DNA μ μ μ μ -
μ (CH₃) μ 5' DNA
DNA μ - (DNA methyltransferases,
DNMTs). 3% μ μ DNA
(Nafee et al., 2008). μ DNA
CpG , “p”
μ μ , μ
μ μ
μ CpG μ . 10% μ CpGs
CpG μ -μ μ
μ μ GC- μ CpG
5
(Bird, 2002). μ μ CpG
, μ
μ μ
(Nafee et al., 2008). CpG
μ μ -μ μ ,
μ μ μμ μ μ .
de novo μ μ μ
μ μ , μ .

CpG (Issa, 2000)
 (Baylin and Jones, 2016, Bird, 2002).
 DNA
 DNA.
 (Bernstein et al.,
 2007).
 DNA
 DNA
 (Gibney and Nolan,
 2010).
 (3)
 DNA. DNMT1
 CpG
 CpG DNA
 DNMT3A DNMT3B
de novo DNA, -CpG
 DNMT1
 DNA.
 DNMT2,
 DNA *in vitro*
 RNA (Goll et al., 2006).
 DNA CpGs
 DNA.
 (Gibney and Nolan, 2010).
 DNA
 TET
 (ten-eleven translocation)
 3 TET1, TET2 TET3

, μ μ μ μ
(Hervouet et al., 2009). μ μ

μ μ DNA. μ μ μ μ
 μ μ μ μ (Wade, 2001) μ
 μ μ , μ

μ μ (Prokhortchouk and Defossez,
2008). μ , p53 DNMT1
 μ DNA μ DNMT1
p21 μ . μ
 μ DNMT1 μ Sp1 Stat3,
DNMT3a μ v-myc, c-myc, ATF2 ATF4, DNMT3b μ Stat-1, v-
myc, Sp1, ATF2 ATF4 (Hervouet et al., 2009). μ
 μ DNA μ
 μ DNMTs μ
 μ μ μ .
 μ μ μ DNA
(DNA methyl-binding proteins, MBDs) ,
 μ μ μ . μ , MBD 1 3
 μ μ μ , μ μ
- .
 μ μ DNA
 μ μ (Wade, 2001).
 μ MBD MECP2. MECP2
 μ μ CpG μ MBD μ
 $\mu\mu$ μ μ
(Newell-Price et al., 2000).
 μ -
 μ Sin3, μ 1 2,
 μ . , MECP2 μ μ
 μ μ μ DNA μ ,
 μ μ μ μ (Delcuve et al.,
2009). MBDs μ
Kaiso, ZBTB4 ZBTB38.

Wnt (Prokhortchouk and Defossez, 2008). Kaiso (Iioka et al., 2009).

3.1.1. DNA

DNA, (Feinberg and Vogelstein, 1983) (7). CpG (Jones and Baylin, 2002). (Feinberg et al., 2006). CpG (Rodriguez et al., 2006). (Howard et al., 2008). R-Ras MAPSI MAGE IGF2 Wilms (Cui et al., 2003).

μ CpG Rb, μ
 μ (Greger et al., 1989),
 μ μ μ p16, MLH1 BRCA1 (Baylin
and Jones, 2016, Jones and Baylin, 2007, Baylin, 2005). ,
 μ μ $\mu\mu$ μ
DNA. μ μ
RUNX3 (Long et al., 2007),
GATA-4 GATA-5
(Akiyama et al., 2003), μ μ
DNA (MLH1, BRCA1,)
. μ
, μ DNA μ
 μ (Guo et al., 2004). μ
 μ μ
 μ μ
(Guo et al., 2008, Guo et al., 2006). DNA μ
 μ μ ,
DNA, μ Wnt, TGF- , NF- μ
 μ μ (Cao et al., 2016, Yan et al., 2014, Yang et al., 2017).
 μ 1.
 μ μ μ
 μ μ μ
 μ . μ CpG
 μ μ μ μ μ DNMTs
 μ μ μ
 μ PML-RAR μ μ
 μ μ μ (Di Croce et al., 2002). , μ
DNA μ μ (Frigola et al., 2006),
 μ μ μ CpG μ μ μ
 μ μ μ μ

polycomb 3 27me3 (Schlesinger et al., 2007, Widschwendter et al., 2007, Ohm et al., 2007)

DNA

(Rodríguez-Paredes and Esteller, 2011).

DNMT3A AML (acute myeloid leukemia).

HSCs (hematopoietic stem cells),

AML (

).

μ

(Shlush et al., 2014).

TET2,

AML μ μ

μ μ μ μ μ (Bejar

et al., 2014, Weissmann et al., 2012).

2.

3.2.

μ μ μ μ μ

DNA μ -μ

(2). μ μ μ

μ μ μ μ μ

(H2A, H2B, H3 H4),

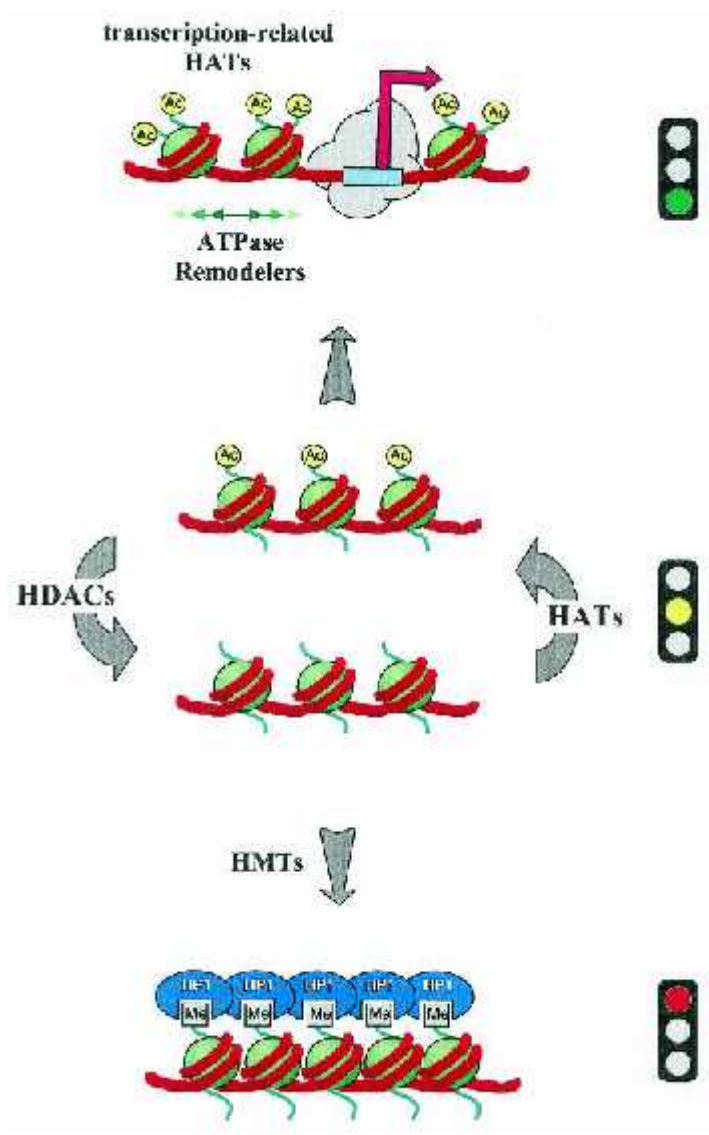
μ 147 DNA. (

, 1) μ DNA μ μ .

μ μ DNA

, μ μ μ
 (Alberts et al., 2003). μ
 μ μ μ
 DNA
 μ (Kouzarides, 2007).
 μ μ μ
 μ - - , μ ,
 μ μ , μ ,
 μ , μ μ μ μ 200
 , μ μ μ , μ ,
 , μ , μ .
 μ μ , μ μ μ μ
 μ (Peterson and
 Laniel, 2004). μ
 ,
 μ μ .
 μ μ μ μ μ μ
 . μ ,
 μ μ μ , μ
 μ μ μ μ , /
 , . μ
 μ μ , ADP- , μ
 μ μ μ μ H3 (Kouzarides, 2007).
 μ μ μ μ μ μ ,
 . μ μ μ
 μ μ μ , μ
 H2A 3, H2B 4 (Henikoff and Smith, 2015).
 μ : 1)
 μ μ μ , μ μ

μ DNA. H μ μ (Greer and Shi, 2012). μ μ μ μ μ μ μ μ μ μ RNA (Greer and Shi, 2012).



μ 6. μ μ μ HATs μ HDACs.

: Eberharter and Becker, 2002

3.2.3.

μ μ ,
μ , μ .
μ μ , μ μ μ
μ .
μ
(Kouzarides, 2000). μμ ,
μ - μ μ μ .
3, 10, μ μ
μ . μ
μ μ μ μ ,
μ μ μ μ
μ (Berger et al., 2009).
μ μ μ μ
μ - μ , μ
DNA (Rossetto et al., 2012, Pérez-Cadahía et al.,
2010, Cohen et al., 2011). μ
H2AX 139
DNA. μ μ -H2AX
μ μ
DNA (Kuo and Yang, 2008).
μ
μ μ μ μ μ
μ . μ μ μ , μ
μ μ μ , μ μ
μ (Cuthbert et al., 2004). μ
μ μ PS2, μ ,
μ PAD4 PS2, μ
.
1 (Denis et al., 2009).

, μ
 μ μ μ μ μ ,
 μ μ , .
 μ μ
 μ μ μ ,
 μ μ .
 μ μ μ μ μ
 μ μ μ μ
 . , μ
 ‘ ’. μ (embryonic stem cells, ESCs)
 μ (. . . H3K4me3)
 (. . . H3K27me3) μ .
 μ μ
 (μ μ)
 (Matsumura et al., 2015, Voigt et al., 2013). μ μ
 μ μ ESCs
 μ μ μ μ
 μ
 μ . ,
 μ μ μ
 (Bernhart et al., 2016).

3.2.4.

μ μ μ μ
 . μ μ
 4 16 (4 16ac) μ μ 20
 4 (4 20me3) (Fraga et al., 2005). ,
 μ HDACs, μ .
 HDACs - (Halkidou
 et al., 2004, Song et al., 2005),

HATs
 HAT CBP p300
 HDACs
 (Yang, 2004).
 (You and Jones, 2012).
 SETD2 MLL2
 93%
 EATL-II (enteropathy-associated T cell lymphoma) 89% FL
 (follicular lymphomas), (Roberti et al., 2016, Morin et al., 2011).
 SETD2
 (Dalglish et al., 2010)
 (Mar et al., 2014).
 EZH2
 (enhancer of zeste 2 polycomb repressive complex 2 subunit)
 PRC2 (polycomb repressive complex 2)
 27. EZH2
 non-Hodgkin,
 H3K27.
 MDS (myelodysplastic syndrome), MPN (myeloproliferative neoplasm),
 ALL (acute lymphoblastic leukemia),
 EZH2

μ μ .
 μ μ μ μ μ μ
 μ μ , μ μ μ μ .
 μ μ μ μ μ
 μ μ IDH1/2 (isocitrate dehydrogenase 1 and 2) μ
 20% μ AML. μ μ
 μ μ . μ μ
 TET2, .
 IDH1/2 TET2 μ μ μ μ
 . μ μ μ IDH1/2
 TET2 μ , μ
 μ μ μ .
 μ μ μ μ μ μ
 μ μ μ μ μ μ
 μ μ (Figueroa et al., 2010).
 μ μ ,
 μ μ μ μ
 (7). μ μ H3K9 H3K27
 μ μ (Nguyen et
 al., 2002, Valk-Lingbeek et al., 2004). μ HMTs
 μ μ μ μ
 μ μ μ μ
 μ , EZH2 μ HMT
 3 27 μ (Valk-Lingbeek
 et al., 2004). μ G9a, HMT 3 9,
 μ μ μ μ
 μ μ μ μ μ (Kondo et al.,
 2008, Kondo et al., 2007). μ μ μ MLL,
 H3K4, μ Hox
 μ μ (Krivtsov and Armstrong,
 2007). μ μ μ HMTs, μ
 μ HMTs (HDMs) μ
 μ μ (Cloos et

al., 2008). LSD1, μ μ , μ
 μ (3 4 3 9
 μ ,), μ (Shi et al., 2004,
 Metzger et al., 2005), μ - - .
 μ HDMs, LSD1, μ
 ,
 μ . , μ μ μ ,
 LSD1 μ μ
 μ *in vitro*
 μ (Schulte et al., 2009).

1. μ μ

1. μ					
μ	p16 (CDK2A)		G1/S	μ	μ , HCC, GC, CRC, , μ
	CHFR		G2/M	μ	NSCLC, GC, CRC, BC, HCC, , μ , μ , μ
	RASSF1A		M	μ	BC, , μ , , , μ , μ μ
	Chk2		2, μ	μ	μ , μ μ Hodgkin's, NSCLC
	ATM		μ	μ	BC, μ μ , μ , μ
DNA	BRCA1	μ	μ	μ	NSCLC, CRC, μ ,
	BRCA1	μ	μ	μ	NSCLC, BC
	FANCF	FA μ	F	μ	NSCLC, , μ ,

	XRCC5	NHEJ μ		μ	NSCLSC, μ
	WRN	BER		μ	NSCLC, CRC, GC, μ μ non-Hodgkin, μ
	MSH2	MMR ATP		μ	μ , HCC
	RAD23B (hHR23B)	NER		μ	μ μ
Wnt μ	WNT5A			μ	CRC
	WNT2		T		CRC
	WIF1	Wnt		μ	HCC, GC, BC, CRC, μ
	DKK	LRP5/6		μ	NSCLC, BC, CRC, GC, HCC
	Cadherin	-		μ	BC, NSCLC, CRC, GC, HCC, ESSC, CLL, ,
	APC	μ	-	μ	GC, CRC, ESCC. BC, NSCLS, HCC
	GSK3	μ	-	μ	CRC
TGF- μ	RUNX3	SMADs		μ	GC, HCC, CRC, BC, μ ,
	SMAD6/7	SMAD3 TGF		μ	μ
	DACH1	NCoR SMAD4		μ	GC, ESS, CRC, HCC, μ , μ
	FBXO32	TGF μ		μ	ESSC, GC
NF-	p65 (RelA)	μ	T		CRC, μ
	ZNF382	NF-		μ	GC, ESCC, CRC, BC

	ZNF545	NF-		μ	HCC
	CXCL14	NF-		μ	CRC
Akt	ADAMTS9	μ	Akt	μ	CRC
	RAI2	μ	Akt	μ	CRC
	HIN-1	μ	Akt	μ	NSCLC
p53	RASSF10	p53 μ		μ	CRC, HCC,
	BCL6B	p53 μ		μ	HCC, CRC, GC
	DLEC1	μ	p53	μ	SCC,
	CRBP1			μ	CRC, ESSC,
	RARbeta2			μ	BC, μ μ ,
Hedgehog	PTCH1			μ	GC, BC, μ μ ,
	SHH	μ		μ	GC, BC
	HHIP			μ	LAC, GC, HCC, μ μ ,
	GLI1	μ	T		BC
	GLI3	μ		μ	GC

: [μ (Guo et al., 2019)]

2.

DNMT1	DNA μ				CRC
DNMT3A	DNA μ				μ , AML
DNMT3B	DNA μ				μ ICF
TET1	5 μ		SNPs μ μ		CRC, CLL
TET2	5 μ				
IDH1/2					AML, μ

ALKBH3					μ DNA	
SETD2					μ , μ , μ ,	
CREBBP					μ , μ , μ ,	
MLL1					ALL, CRC, GC, μ μ	
EP300		H3K4			ALL, AML, - μ μ ,	
DOT1L					μ , GC,	
EZH2		H3K27			μ , μ - μ μ ,	
NSD1					CRC, GC, μ , AML, HCC, μ	
HDAC10					μ	
JMJD1C		μ H3K4/H3K9				
ATRX					SWI/SNF	
CHD5	ATP				NURD μ BC, CRC, μ , μ , μ , μ	
HELLS	μ				CRC, GC, NSCLC	
SMARCB1	μ				BAF μ BAF μ , μ , μ	
ARID1A	μ				HCC, GC, CRC, BC, μ , μ , μ , μ	
SMARCA4	ATP				BAF μ , μ , μ , μ , μ , μ ,	
SAT2		μ 2	μ	μ	BC, GC, HCC, μ	
ALU		μ	μ	μ	BC, CRC, GC, μ	
LINE-1		μ		μ	CRC, BC, μ , μ , μ ,	
MBD4		μ		μ	CRC,	

MGMT	μ μ 6- μ	μ	NSCLC, CRC, GC, μ μ μ ,
TDG	DNA	μ	μ μ
NEIL1	μ μ 8-	μ	CRC, NSCLC,
OGG1	DNA	μ	BC, CRC
XPC	μ DNA	μ	
XPG	μ ERCC5/XPG/Rad2 NER μ	μ	CRC,
MLH1	MR ATP , μ μ μ	μ	ESCC, GC, CRC, NSCLC, , , , μ / μ μ , -

: [μ (Guo et al., 2019)]

3.3. RNAs

ncRNAs

μ μ ,
 μ - μ

μ μ

μ (2).

μ μ RNAs μ ,

μ . μ ncRNAs
(. . siRNAs, miRNAs,
piRNAs) μ (long non-coding RNAs, lncRNAs) μ
 μ 200 μ , (Wei et al.,
2017). 3 μ RNAs

3. μ RNA μ

μ	(bp)	RNA	μ
siRNA	19-24	RNA	μ

miRNA	19-24	pri-miRNA	μ
piRNA	26-31	μ	μ DNA ,
lncRNA	> 200		μ X- μ μ

: [μ (Wei et al., 2017)]

μ siRNAs miRNAs, μ μ
μ (19-24) μ μ Dicer,
μ μ μ
RNA μ μ μ
Argonaute (AGO) (Ferreira and Esteller, 2018). μ
siRNA μ μ μ
μ DNA (Morris et al., 2004, Bayne and
Allshire, 2005). cisplatin-
μ μ , siRNA
μ EZH2 (Zhou et al., 2015).
μ μ Dicer, Argonaute RNA-
μ μ RNA μ Rdp1,
μ RISC, ncRNAs, μ μ
H3K9me μ μ (Hall
et al., 2002, Volpe et al., 2002).
miRNAs μ
RNA μ ,
siRNAs. 50% μ μ
μ . μ μ μ miRNAs
μ μ μ μ μ AGO,
μ miRNA mRNA- (Bartel, 2009). μ
μ miRNAs μ μ μ RNA-
, mRNA μ μ
μ . miRNAs μ
μ μ μ mRNA
miRNA μ (Bartel, 2009, Rajewsky, 2006,
Lewis et al., 2005). 13000

CpG, miRNAs (Lewis et al., 2005).
 HDAC4 miR-140
 (Tuddenham et al., 2006).
 DNMT3A DNMT3B miR-29
 Dicer.
 Rbl2 DNMT3A DNMT3B Rbl2 miR-29,
 Dicer (Benetti et al., 2008, Sinkkonen et al., 2008).
 miR-29
 piRNAs (PIWI-interacting RNAs) 26-31
 ncRNAs
 PIWI
 (Lau et al., 2006, Grivna et al., 2006).
 RNA
 Piwi/piRNA *de novo* DNA (Aravin et al., 2008). Piwi
 HOX PcG
 PcGs, polycomb
 piRNAs Piwi
 (Lin, 2007). piRNAs
Drosophila melanogaster
 (Yin and Lin, 2007). Piwi
 HP1a

(Huang et al., 2013). , μ Piwi/piRNA μ RNA μ II
 μ piRNA μ
DNA μ (Kuramochi-Miyagawa et al., 2008).
 μ lncRNAs μ RNA
 μ , μ : μ RNAs,
 μ μ RNA (small nucleolar RNA, snoRNA),
 μ μ μ (Batista and
Chang, 2013). μ μ
 μ μ , $\mu\mu$
 μ μ , μ lncRNAs
 μ μ μ , μ μ
 μ μ μ μ μ μ . ,
 μ lncRNAs μ - μ μ ,
mRNA, μ .
 μ μ
DNA, DNA μ DNA (Marchese et al.,
2017).

3.3.1 RNAs

ncRNAs μ μ
, μ μ μ μ μ
. μ miRNAs
miR-21, miR-155, miR-210 miR-221,
 μ μ
 μ μ . ,
miRNAs miR-34 miR-200
 μ . μ miRNAs μ
, μ (Lu et al., 2020).
 μ , miR-181 μ
 μ ,

(Rezaei et al., 2020) (7).

miR-181

miRNAs

miR-200

ZEB1 ZEB2

EMT (Hurteau et al., 2007, Gregory et al., 2008, Park et al., 2008).

CLL (chronic lymphocytic leukemia)

13q14

miR-16 miR-15

(Calin et al., 2002).

miRNA

Drosha Dicer1

(Lin et al., 2010, Merritt et al., 2008).

ncRNAs

ncRNAs

miRNAs

miR-34b/c, miR-148 miR-9-3

(C-MYC, E2F3, CDK6, TGIF2)

(Lujambio et al., 2008).

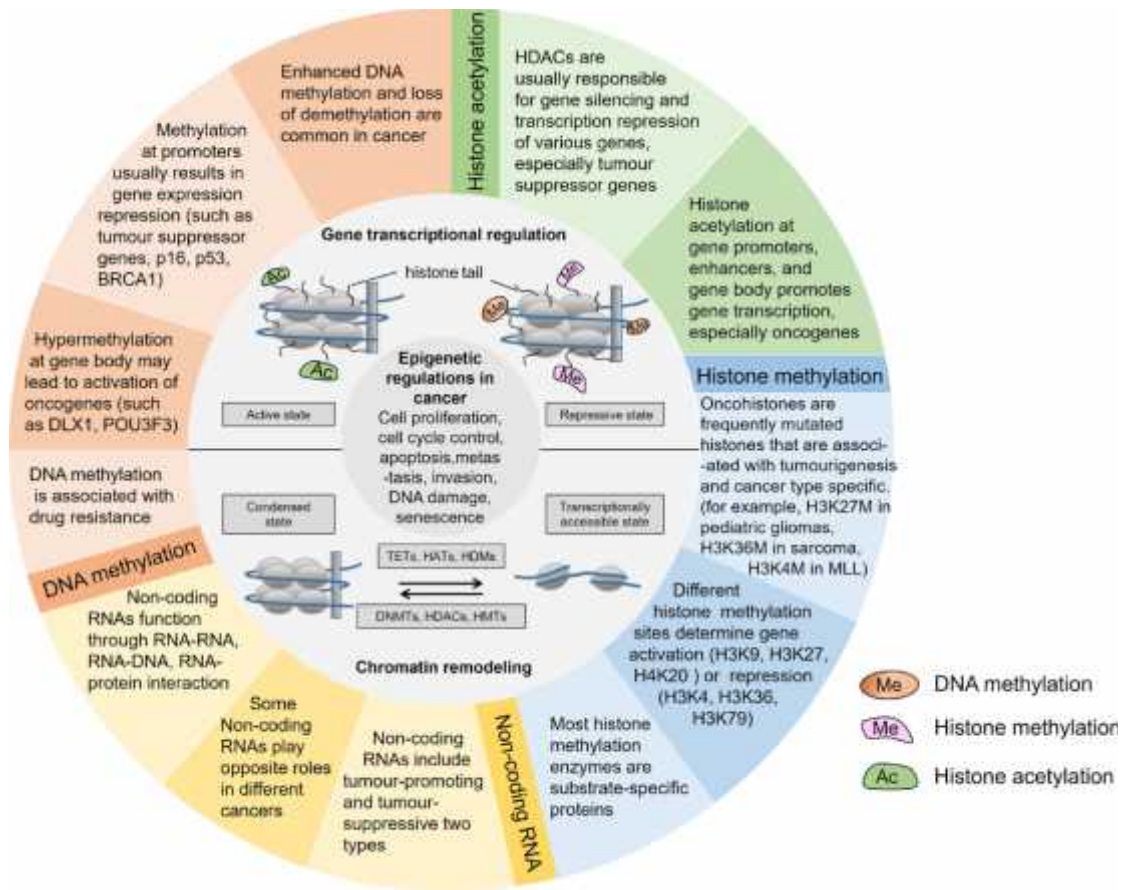
ncRNAs

(Fabbri et al., 2007), AML (Garzon et al., 2009a).

miR-29 DNMT3A

DNMT3B μ - μ μ (Fabbri et al., 2007).

miR-29b μ μ μ
DNA (Garzon et al., 2009b). miR17-5p miR-20a
 μ μ μ ,
 μ μ μ μ
 μ (Gonzalez et al., 2008).
, miR-200 μ μ
DNMTs μ μ μ H3K27 EMT
(Davalos et al., 2012, Vrba et al., 2010, Wiklund et al., 2011).
lncRNAs circRNAs μ miRNAs μ μ
 μ (Guil and
Esteller, 2015). μ μ
lncRNA FAM83H-AS1 μ miR-136-5p
 μ MTDH ,
 μ , μ
 μ (Han et al., 2020). circRNA circFUT8
 μ
miR-570-3p/KLF10 (He et al., 2020). , μ
-6 μ pri-miRNAs
mRNAs . μ “writers” METL3
METL14 μ ,
 μ μ μ mRNA
 μ -6 μ (Pan et al., 2018).
, μ pri-miRNA μ
DGCR8 μ μ -6 μ
HCC (Alarcón et al., 2015).
 μ lncRNAs μ miRNAs ,
HOTAIR (Hox transcript antisense intergenic RNA)
 μ μ μ 1
miR-326, μ μ P13K/Akt
MEK1/2 μ (Ke et al., 2015).



7. μ μ μ
 μ , ,

: Cheng et al., 2019

(Schaefer et al., 2009).

, μ μ μ (Lu et al., 2020).

μ , μ μ μ , μ μ ,
zevularine (ZEB), 6- 4- -2 . ZEB
2-(1)- μ μ DNMTs
 μ μ μ μ μ DNMTs 6
 μ μ DNA (Zhou et al., 2002).

μ (CD), ZEB
 μ μ μ μ
(Holleran et al., 2005). , ZEB μ μ

μ μ DNA μ μ
 μ (Cheng et al., 2004b, Tan et al., 2013). ZEB
 μ - μ

μ DNMTIs DNMTIs
(Cheng et al., 2004a). μ , p16 μ -
 μ DNA μ

. , μ
ZEB, μ μ μ (Peng et al., 2015). , μ μ

, AML EBV-
Burkitt's μ μ (Takemura et al., 2018).

μ - ,
 μ μ DNMTs -
 μ DNMTs μ μ

CpG. μ
, EGCG, RG108, MG98, disulfiram, . μ
 μ μ μ μ μ

. MG98 μ
3'UTR DNMT1

DNA	μ	μ	μ	μ	μ	μ	μ
(Vidaza®)				MDS, AML		FDA	μ
		()		AML		III	
(Dacogen®)				MDS, AML		FDA	μ
		(talacotuzumab)		AML		III	
Disulfiram		()		μ		II	
EGCG		()		PC		II	
Hydralazine		(magnesium valproate)			μ	II	
SGI-110				HCC		II	
		(pemetrexed, cisplatin, gefitinid)		NSCLC		II	
6-thioguanine		(dexamethasone, cyclophosphamide, vincristine,)		μ μ		IV	
4-thio-2-deoxycytidine				μ		I	
MG98				μ		I	
: [μ (Lu et al., 2020)].							

4.2.

& μ

μ μ DNA,
 μ , μ μ μ μ
, μ μ μ
 μ , μ μ .
,
 μ 3 4 μ
 μ H3K9 μ (Mutskov and Felsenfeld,
2004). μ , HATs
“writer” μ - μ , HDACs
“eraser” μ - μ . μ
bromodomains (BRDs)
 μ - μ
 μ μ BRDs “readers”
 μ μ μ .
bromo- and extra-terminal (BET) μ μ
BRD2, BRD3, BRD4 μ BRDT. BET
 μ μ μ μ
 μ μ μ
 μ (Muddassir et al., 2021).
 μ
 μ .

4.2.1

HATs BETs

HATs BETs
 μ , μ μ
HATs μ μ μ
 μ μ . μ ,
BRD μ μ ,
 μ HATs (Cheng et al., 2019).

p300 TIP60. μ μ μ HATs: μ PCAF,
 μ (Ac-CoA) μ μ
 (Lau et al., 2000, Yang et al., 2014). ,
 μ , μ μ μ
 μ μ . μ -
 μ . μ μ
 μ garcinol, μ
 (Balasubramanyam et al., 2003, Balasubramanyam et al., 2004b,
 Balasubramanyam et al., 2004a). HAT
 μ .
 μ . -
 methylene-g-butyr-olactones μ μ HATs μ
 GCN5L2 PCAF (Biel et al., 2004). Isothiazolone
 HAT p300 PCAF (Stimson et al., 2005).
 μ HAT μ .
 HATs, thiazide sulfonamide C646
 μ μ .
 μ H
 μ HATs
 HATs. μ ICG-
 001 PRI-724. , μ HAT
 μ
 . CTPB μ
 p300, μ μ μ (Balasubramanyam
 et al., 2003). TTK21 SPV106
 (Cheng et al., 2019).
 BRDs μ μ
 μ μ
 μ JQ1 I-BET762
 BET. JQ1 μ μ μ
 BRD4 μ ,

BRD4-NUT, μ μ
(Filippakopoulos et al., 2010). μ ,
BRD4 I-BET762 (Nicodeme et al., 2010). ,
BET: MS417, OTX-015,
RVX-208, OXFBD, I-BET151, PFI-1, MS436 XD14 (Brand et al., 2015).
 μ -BET BRD μ μ μ «WFP
shelf” - (gatekeeper) C
(Romero et al., 2016). HATs BRD Gcn5, PCFA,
p300 CBP. CBP μ MS2126, MS7972,
ischemin, SGS-CBP30 I-CBP112. μ 1-(1H-indol-1-yl)
ethanone μ μ CBP
p300 (Xiang et al., 2018). BRD BAZ2A/B μ
BAZ2-ICR GSK2801. LP99
BRD9, 200 BRD9
BRD7, 700 BRD9 μ
 μ BET (Theodoulou et al., 2016). PFI-3
SMARCA4 PB1, μ μ μ .
BRPF1 μ BRPF,
 μ MYST. BRPF1 μ PFI-4,
OF-1 NI-57. 1,3-dimethyl benzimidazolones μ
BRPF1. PFI-4 OF-1 1,3-dimethyl
benzimidazolone. NI-57 OF-1 μ BRPF1
3 . IACS-9571
TRIM24 BRPF1 (Palmer et al., 2016). , bromosporine
BRD μ ,
 μ BET (Picaud et al.,
2016).

5. μ μ μ μ

μ	/
HDAC	

Abexinostat (PCI-24781) μ μ &

	(doxorubicin)	μ , μ μ &
CUDC-101		μ
Belinostat (Beleodaq /PXD101)		PTCL, HCC, μ μ μ Burkitt, DLBCL FDA MDS, μ , &
Entinostat (SNDX-275)	(paclitaxel, carboplatin) (entinostat, exemestane, placebo)	BC II
Givinostat (ITF2357)		& μ
Mocetinostat (MGCD0103)		II μ μ
Panobinostat (LBH-589)		MM, μ μ μ AML μ , RCC, BC, FDA μ μ Hodgkin's, III (Placebo)
Pracinostat (SB939)		MLD II MLD II (ruxolitinib)
Romidepsin (Depsipeptide/FK228)		CTCL, PTCL μ FDA PTCL
Valproic acid (VPA)	(alisertib, pralatrexate, gemcitabine) (azacytidine, all-trans retinoic acid)	MDS, AML II
Vorinostat (SAHA)		CTCL μ FDA
	(KW-0761)	AML III

BET

I-BET762 (GSK525762/molibresib)		μ	
	(abiraterone, enzalutamide, prednisone)	μ	
OTX-015 (MK-8628)		AML, DLBCL, ALL, MM	
TEN-010 (RO6870810)		μ	
	(atezolizumab, daratumumab, venetoclax, rituximab)	μ	MM
CPI-0610	(ruxolitinib)	MDS	, AML, I & II
FT-1101	(azacytidine)	AML, μ μ	non-Hodgkin
ZEN003694	(talazoparib)		BC II
BMS-986158		μ μ ,	
	(nivolumab)	μ	
ABBV-075	(vnenetolacx)	μ μ	
GS-5829	(exemestane, fulvestrant)	μ μ μ	,
PLX51107	(azacitidine,)	AML, MDS BRD4	
	: [μ (Lu et al., 2020)]		

4.2.2. HDACs

HDACs μ
70 ,
 μ

1977). , μ (Riggs et al., (TSA) μ HDACs, (Yoshida et al., 1990).

μ HDACs, SAHA TSA μ μ μ p21, p27 NF- , MG132 μ TSA (Fandy et al., 2005). HDACs μ μ μ (Fang, 2005, Singh et al., 2005). μ μ HDAC μ 5 : , μ , μ , μ . μ , μ μ μ 5 μ HDACs.

μ valproic acid (VPA), AN-9 (pivaloyloxymethyl butyrate). μ μ mM (micromolar). μ μ μ 10 μ TSA SAHA μ - HDACs μ μ μ μ HDACs, μ μ μ μ (Finnin et al., 1999). μ μ , μ μ μ (Yoshida et al., 1990). HMBA (hexamethylene bisacetamide) μ (HPCs), 2 HPCs oxamflatin, SAHA, suberic bishydroxamic acid (SBHA) m-carboxycinnamic acid bishydroxamide (CBHA) HDACs μ 1 (Richon et al., 1998). Oxamflatin, scriptaid amide TSA μ (Jung et al., 1999, Kim et al., 1999, Su et al., 2000). μ MS-275, MGCD0103 CI-994

SK7041 splitomicin HDACs sir2-like

sirtuins, HDACs. nicotinamide

sirtuin μ μ

sirtuins. μ

μ NAD+ μ sirtuins μ

μ

cambinol, salermide, tenovin, EX-527, suramin AGK2 sirtuins

(Cheng et al., 2019).

μ 2 HDACs

μ [vorinostat (SAHA), belinostat (PXD101), LAQ824

panobinostat (LBH589)] μ [entinostat (MS-275), tacedinaline(CI-994) mocetinostat (MGCD0103)] μ

romidepsin

μ μ μ -

HDACs μ . 2006, SAHA

FDA μ

μ μ - (Mann et al., 2007). 2009, romidepsin 2

μ HDAC. μ μ

μ μ . belinostat

(Beleodaq PXD101) 2014 FDA

μ μ - . , panobinostat,

μ - HDAC . μ μ

FDA

μ μ μ . μ μ

μ HDAC2,

HDACs (Cheng et al., 2019,

Daigle et al., 2011). μ

μ HDAC . μ

4.2.3. HMTs HDMTs

DOT1L

EPZ004777, μ μ μ μ MLL
 μ (Daigle et al., 2011).
 μ , 2 . EPZ-
5767 μ -
(Daigle et al., 2013). EPZ-5767 μ μ
cytarabine, daunorubicin DNMT
ALL μ μ MLL. EPZ-5767 μ μ
 μ μ μ MLL (Basavapathruni et al., 2014).
, EZH2, μ μ μ
3-deazaneplanocin A (DZNep), neplanocin-A.
 μ , DZNep SAH
EZH2 SAH, μ
PRC2 μ μ μ (Miranda et al., 2009, Glazer et al.,
1986). SAM.
SAM μ μ μ . 1
 μ μ EZH2,
EZH2 μ μ μ μ SAM (Qi et
al., 2012). GSK343 GSK126
SAM μ (Verma et al., 2012, McCabe et al.,
2012). EPZ005687 EZH2, μ
 μ μ H3K27 μ μ μ μ
 μ Tyr641 Ala677 EZH2 μ μ
 μ (Qi et al., 2012).
EPZ6438, μ μ
 μ μ μ (Knutson et al., 2014). CPI-1205
 μ EZH2 .
TCP MLL-AF9 μ
(Harris et al., 2012). TCP
 μ μ μ μ all-trans
(ATRA) μ 3 4me2
 μ μ (Schenk et al., 2012) .
TCP μ

, μ μ μ OG-002, RN-1, SP2509 GSK690
(Liang et al., 2013, Neelamegam et al., 2012, Fiskus et al., 2014).

LSD1, o -1001 μ
 μ ,
 μ MLL, μ μ (Maes et al.,
2015). TCR -1001 LSD1

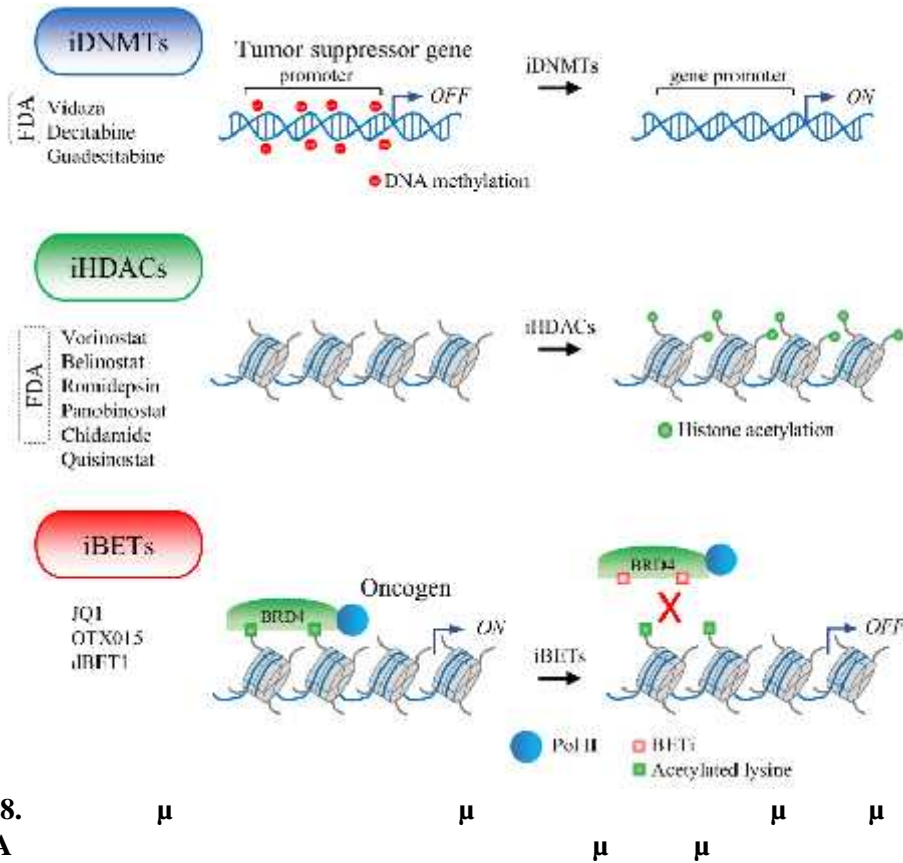
GSK2879552, μ μ
 μ . Daminozide [N-(dimethylamino succinamic acid)]
 μ μ KDM2/7
 μ μ μ μ μ μ (Rose et al.,
2012).

Daminozide siRNA μ KDM7
 μ μ μ H3K9 (Tan
et al., 2014). GSK-J1 1 μ KDM6 μ
 μ μ
 μ (Kruidenier et al., 2012).

μ μ KDM6 μ KDM5,
GSK-J4 KDM5B KDM4C
(Heinemann et al., 2014). KDM5B, EPT 103182,

μ μ
 μ μ μ μ . KDM8 JMJD6
 μ μ μ ,
NOG (Maes et al., 2015). μ

μ μ μ μ ,
 μ .



8. DNA : Roberti et al., 2019

4.3. RNAs & miRNAs

miRNAs anti-miRNAs miRNAs

miRNAs miRNA *in vitro*,
 1 siRNA patisiran

FDA 2018 mRNA transthyretin (Wood, 2018).
 miRNA

miR-34a (MRX34), MRG-201, MRG-106, RG-012, RGLS5579

targomiRs. miRNA miRNA

miRNA-34a PC,

NSCLC ALL CD44, PD-L1, ZEB1 BCL-2. MRX34 μ miR-34a (Hanna et al., 2019). μ miRNAs μ , μ antagomiR miRNAs μ μ μ . antagomiR-24 μ CTCL, μ . JQ1 μ μ miR-214, μ miR-214 (Kohnken et al., 2019). lncRNAs μ μ . μ μ μ lncRNAs, μ μ μ μ lncRNA PCA3 (Lee et al., 2014). lncRNA MALAT1, NEAT1, UCA1 ANRIL μ μ (Gutschner et al., 2013). μ μ antisense μ μ lncRNA μ μ (Arun et al., 2018). μ μ μ ncRNAs, μ μ μ .

6. RNAs μ μ μ μ μ -

μ		/	
MesomiR-1 (miR-16)		NSCLC, μ μ	
Miravirsen (miR-122)		C	II
MRX34		SCLC, μ μ , ,	I

(Shahbazi et al., 2016, Harding et al., 2018).

μ , μ

μ

μ

μ

μ , μ cisplatin

MLH1, (Zeller et al., 2012).

MEST MDK

μ

μ

μ

cisplatin μ - μ

μ , μ

μ μ μ

μ μ μ

-

μ HCC

mRNA HDAC3 HDAC5 μ

HDACs μ LBH-589 μ

H3 HSP90 CDH1, e-cadherin (Zeller et al., 2012).

μ μ sorafenib, μ

FDA μ μ , resminostat, μ

HDACi μ HDAC1/2/3, μ

μ μμ

μ HCC, μ μ μ μ resminostat (Bitzer et al., 2016).

μ (ICIs)

μ μμ . PD-1/PD-L1 CTLA-4 μ ICIs

μ , μ

μ , μ T-

μ , μμ μ .

μ MHC-I

μ μ

μ guadecitabine, DNMT1, μ

MHC-I CD8+ T

μ (Luo et al., 2018).

μ

PD-1 μ . μ

μ CD8+ T- PD-L1
 μ μ DNMT3 μ
 μ - (Ghoneim et al., 2017).
 μ μ anti-PD1 , μ
 μ T-
, μ ,
 μ , μ μ , (Ghoneim et al., 2017, Zhu et al.,
2016). , μ 4SC-202,
 μ μ μ μ , HDAC1 3
LSD1 μ μ μ mM,
 μ (Cheng et al., 2019).

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