



Review Article



Targeting Histone Modifications in Colorectal Cancer: Therapeutic Potential of Epigenetic Modifiers on Acetylation, Methylation and Phosphorylation

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Received: April 16, 2025 | Revised: June 19, 2025 | Accepted: July 21, 2025 | Published online: January 07, 2026

Abstract

Colorectal cancer (CRC), like all other cancers, results from genetic and epigenetic alterations of the genome. The mechanisms leading to epigenetic alterations include DNA methylation, histone modifications, and small non-coding RNAs. As shown in many studies, some histone modifications such as acetylation, methylation, and phosphorylation are reported to be altered in CRC. Since these epigenetic alterations are reversible, they can be targeted as a strategy for CRC treatment. Numerous studies demonstrate the effects of molecules (both natural and synthetic) as inhibitors of enzymes responsible for histone acetylation, methylation, and phosphorylation in CRC cell lines. Some of these molecules have reached clinical trial stages. Vorinostat and belinostat, as histone deacetylase inhibitors; pinometostat and ribavirin, as histone methyltransferase inhibitors; and staurosporine and barasertib, which target histone phosphorylation, are among the promising epigenetic modifiers targeting histone alterations. Some of these modifiers can be used alone or in combination with other anticancer drugs or radiotherapy to increase efficacy. This review aims to identify molecules that target enzymes responsible for altering acetylation, methylation, and phosphorylation of histones in CRC.

Introduction

Cancer, in particular colorectal cancer (CRC), is a result of genetic and epigenetic dysregulations.¹ The epigenetic modifications that can be caused by three main mechanisms, DNA methylation, histone modifications, and non-coding RNAs, lead to the alteration of the expression of genes involved in cancer (oncogenes and tumor suppressor genes (TSGs)).² Researchers increasingly believe that, since epigenetic alterations are, unlike genetic alterations, reversible, they could be a promising target for the development of novel anticancer therapies. In fact, molecules that can inhibit these alterations may restore the normal expression of oncogenes and TSGs. DNA methyltransferase inhibitors (DNMTis) that target DNA methylation alterations, and histone deacetylase (HDAC) inhibitors (HDACis) that target histone acetylation, are the most studied

in this sense. Some of these molecules are already approved for use in the treatment of certain cancers. Decitabine (used in the treatment of myelodysplastic syndrome) and 5-azacytidine (used in the treatment of acute myeloid leukemia) are among the DNMTis.³ Additionally, among HDACis, vorinostat and belinostat are both used in the treatment of hematological cancers with less severe side effects.⁴

In this review, we first highlight the most extensively studied alterations of histone acetylation, methylation, and phosphorylation involved in CRC. We then propose a selection of molecules that may serve as epigenetic modifiers, either alone or in combination, targeting these alterations in the treatment of CRC.

Histone modifications in CRC

Histones are a family of basic proteins that are rich in lysine and arginine, around which DNA filaments are tightly wrapped to form chromatin in the nucleus of eukaryotic cells. Besides DNA methylation, histone modification is one of the most studied epigenetic mechanisms. It has been well demonstrated that histone modifications play a key role in the pathogenesis of many diseases, particularly cancer.⁵ Additionally, it has been reported that acetylation and methylation of lysine and arginine residues of histones are

Keywords: Colorectal cancer; Epigenetic alterations; Histone acetylation; Methylation; Phosphorylation; Epigenetic modifiers.

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How to cite this article: Jaafari A. Targeting Histone Modifications in Colorectal Cancer: Therapeutic Potential of Epigenetic Modifiers on Acetylation, Methylation and Phosphorylation. *Gene Expr* 2026;25(1):e00046. doi: 10.14218/GE.2025.00046.

associated with the clinicopathological features of CRC. For example, methylation of lysine 9 on histone H3, acetylation of lysine 27 on H3, and acetylation of lysine 12 on H4 have been shown to be increased in CRC tissues compared to normal mucosal cells.⁶ On the other hand, according to the results of chromatin immunoprecipitation analysis performed on circulating nucleosomes, trimethylation of lysine 9 on H3 and trimethylation of lysine 20 on H4 were shown to be decreased in patients with CRC compared to healthy individuals.⁷ Other epigenetic alterations of histones reported to be involved in CRC include phosphorylation (decrease of phosphorylation of Histone H3 at Ser10 (H3S10ph) and increase of H2AX),^{8,9} sumoylation (decrease of SUMO E1 and E3, and the sole SUMO E2 enzyme Ubc9),¹⁰ ADP-ribosylation (H3R117 mono-ADP-ribosylation),¹¹ neddylation (Ned HuR and Ned NF- κ B),¹² and ubiquitination (decrease of H2Bub1).^{13,14} Table 1 below summarizes some of the most extensively studied epigenetic modifications of histones involved in CRC.^{15–33}

Epigenetic modifiers of histone alterations in CRC

Epigenetic modifiers of histone acetylation in CRC (HDAC and histone acetyltransferase (HAT) inhibitors)

Histone acetylation

The entire genome of a eukaryotic organism is condensed into chromatin in the nuclei. The basic unit of chromatin, called the nucleosome, is made up of 147 DNA base pairs wrapped around a core protein octamer called histone.³⁴ These proteins include histones H2A, H2B, H3, and H4. Histone H1, located outside of the core octamer, can regulate chromatin fibers in higher-order structure.³⁵ Heterochromatin, which refers to condensed (closed state) chromatin, and euchromatin, which refers to loosely packed (open state) chromatin, are the two major higher-order structures of chromatin. Euchromatin is more accessible to transcription factors and RNA polymerase.^{35,36} Thus, alteration of chromatin state by DNA methylation or histone modifications impacts gene expression by making certain genes more or less available for transcription.^{37–39} Histone acetylation, the most studied mechanism of histone modifications, plays a key role in the regulation of gene expression.^{39,40} In fact, the acetylation of lysine residues (Kac) on histone tails neutralizes the positive charge on the ϵ -amino group of the lysine residues, leading to the unwinding of tightly coiled heterochromatin, which makes the chromatin be in an accessible state (euchromatin).⁴¹ Additionally, the inner pore space of chromatin is increased by histone acetylation, which alters spatial distance and accessibility during interphase, and ensures sufficient space for local initiation and elongation.^{42,43}

HATs and HDACs are the enzymes responsible for histone acetylation and deacetylation, respectively. It has been confirmed that HDACs are expressed by different types of tumors and are involved in carcinogenic events, such as chromosomal translocation-mediated oncogenic protein fusion.^{44,45}

Classification of HDACs and HATs

Eighteen (18) human HDACs have been identified and divided into four (4) classes. HDAC class III is nicotinamide adenine dinucleotide (NAD)⁺-dependent, while classes I, II, and IV are zinc-dependent.⁴⁶ The identified HATs include the P300/CBP, GNAT, MYST, P160, PCAF, and TAFII230 families.⁴⁷ The different HDACs are classified according to their respective length and molecular weight in the following diagram (Fig. 1).

HDACs and HATs involved in CRC

Table 2 below summarizes the histone acetylation enzymes (HDACs and HATs) reported to be involved in CRC.^{48–58}

Epigenetic modifiers of histone acetylation in CRC

HDAC inhibitors in CRC

Many preclinical studies and clinical trials have reported the important effect of HDACis as therapeutic agents in different cancers. These epigenetic modifiers can significantly limit tumor growth, restrain aberrantly proliferated vessels,⁵⁹ induce DNA damage, cell cycle arrest, apoptosis, and autophagy to promote cancer cell death.⁶⁰ It has been shown that HDACis can inhibit the proliferation of different trans

formed cells *in vitro* such as lymphoma, leukemia, myeloma, and non-small cell lung carcinoma. They can also stop tumor progression in many solid and hematological tumors. In addition, these HDACis can modulate the immune response and decrease angiogenesis.⁶¹

Vorinostat (SAHA)

Vorinostat (N-hydroxy-N'-phenyl-octanediamide) was among the first HDAC inhibitors approved by the FDA in 2006 to treat CTCL (cutaneous T-cell lymphoma) (Fig. 2). Vorinostat inhibits all classes of HDAC enzymes except class III.⁶² It has been reported that this molecule has a promising effect on gastrointestinal cancers and metastatic CRC in combination with 5-fluorouracil (5-FU). Vorinostat has an ID₅₀ of 10 nM and 20 nM for HDAC1 and HDAC3, respectively. Vorinostat induces cellular apoptosis.⁶³

Valproate (VPA) (an HDACi and DNMTi)

Valproic acid is a drug used for the treatment of seizure disorders, including epilepsy (Fig. 2). It acts as an inhibitor of GABA transaminase, leading to the blocking of voltage-gated sodium channels and T-type calcium channels.⁶⁴ Recently, it has been reported that this molecule could affect chromatin remodeling. In fact, VPA can alter gene expression through epigenetic marks such as histone acetylation and DNA methylation.^{64,65} It has been demonstrated that VPA can bind to class I HDAC catalytic sites and inhibit their activity, which leads to histone acetylation, in particular at the lysine 9 residue of histone H3 and the lysine 8 residue of histone H4.⁶⁶ H4 hyperacetylation activates cell cycle arrest and apoptosis. VPA can also promote proteasomal degradation of HDAC2. In fact, it has been shown that in the HeLa (human cervical carcinoma) cell line, histone H4 hyperacetylation induced by treatment with 3.0 mM VPA for 24 h led to upregulation of more than 1,074 genes, some of which are related to the cell cycle, cell signaling, pyruvate dehydrogenase kinase 4, and ATPase class V, and downregulation of 551 genes including those related to importin β , Fas apoptotic inhibitory molecule, and cyclin B1.⁶⁷ In another study, in rat neurons treated with VPA, hyperacetylation of H3 and H4 was found only in the promoters of 726 upregulated genes, including genes involved in epileptogenesis.⁶⁸

Regarding the role of this molecule in CRC, Strey *et al.*⁶⁹ reported that VPA exerts an anti-neoplastic effect in many colorectal tumor cell lines (Caco-2, SW-480, CX-1, and WIDR) *in vitro* by altering cell cycle regulation (cycle proteins cdk1, cdk2, cdk4, cyclin D, cyclin E, p19, p21, and p27 were altered). In fact, this molecule inhibits cell growth and induces cell cycle arrest by the upregulation of H3 and H4 acetylation. Furthermore, tests *in vivo*

Table 1. Histone modifications involved in CRC

Histone modification	Status in CRC tissue compared to normal tissue	What the histone modification is associated with	Reference
<i>Histone acetylation</i>			
Global acetylation of H3 (Global H3ac)	Increased	Poor overall survival and poor prognosis	15
Global acetylation of H4 (Global H4ac)	Decreased	Well differentiation and Progression of CRC	16
Acetylation of lysine 27 on H3 (H3K27ac)	Increased	Promotes cell proliferation and differentiation	17
Acetylation of lysine 12 on H4 (H4K12ac)	Decreased	Progression of CRC	18
Acetylation of lysine 9 on H3 (H3K9ac)	Decreased	Significantly associated with the histological type of CRC	19
Acetylation of lysine 18 on H3 (H3K18ac)	Decreased	Progression of CRC	18
Acetylation of lysine 56 on H3 (H3K56ac)	Decreased	Better survival of CRC patients and a lower chance of tumor recurrence	20
Acetylation of lysine 16 on H4 (H4K16ac)	Decreased	Better survival of CRC patients and a lower chance of tumor recurrence	16,21
<i>Histone methylation</i>			
Methylation of lysine 9 on H3 (H3K9me3)	Increased	Specifically elevated in aggressive CRC tissues and positively correlated with lymph node metastasis in CRC patients	22
Dimethylation of lysine 4 on H3 (H3K4me2)	Increased	High H3K4me2 is dramatically associated with CRC clinicopathological factors, including deeper tumor invasion and advanced pathological stage	15
Trimethylation of lysine 4 on H3 (H3K4me3)	Decreased	Associated with transcriptionally active genes and may lead to genomic instability associated with variant enhancer loci in the CRC transcriptome	21,23
Dimethylation of lysine 9 on H3 (H3K9me2)	Increased	Poorer overall survival time of patients with gastric cancer	24
Dimethylation of lysine 27 on H3 (H3K27me2)	Increased	The H-scores of H3K27me2 were lower in the liver metastases than in the corresponding primary tumors. H3K27me2 in the primary tumors correlated with tumor size. Lower levels of H3K27me2 in the primary tumors correlated with poorer survival rates ($P = 0.039$)	25,26
Trimethylation of Lysine 27 on H3 (H3K27me3)	Increased	Positively correlated with the metastasis-free survival of CRC patients and a low H3K27me3 level predicted a poor outcome upon chemotherapeutic drug treatment	25,27
Dimethylation of lysine 36 on H3 (H3K36me2)	Decreased	H3K36me2 in the primary tumors correlated with histological type ($P = 0.038$), and lymph node metastasis ($P = 0.017$)	25,26
Dimethylation of lysine 79 on H3 (H3K79me2)	Increased	High <i>DOT1L</i> expression and H3K79me2 levels were associated with poor patient survival	28,29
Dimethylation of lysine 20 on H4 (H4K20me2)	Decreased	The low level of H4K20me2 was a common hallmark in CRC cell lines	16
Trimethylation of lysine 20 on H4 (H4K20me3)	Decreased	Levels of H4K20me3 were lower in patients with CRC than in individuals with normal colonoscopy and those with pre-cancerous polyps ($P = 0.02$ and $P = 0.01$, respectively)	22,30
<i>Histone phosphorylation</i>			
H3S10ph (Phosphorylation of Serine 10 on H3 by Aurora B kinase (AURKB))	Increased	Expression of <i>AURKB</i> promotes the growth and proliferation of CRC cells through H3S10ph in the promoter region of Cyclin E1	31
H2AX (Phosphorylation of H2A)	Increased	Phosphorylation of <i>H2AX</i> to γ -H2AX is induced by DNA DSB and is associated with the development of colorectal cancer	32,33

ac, acetylation; CRC, colorectal cancer; DSB, double-strand break; H, histone; me, methylation; ph, phosphorylation.

HDACs classification

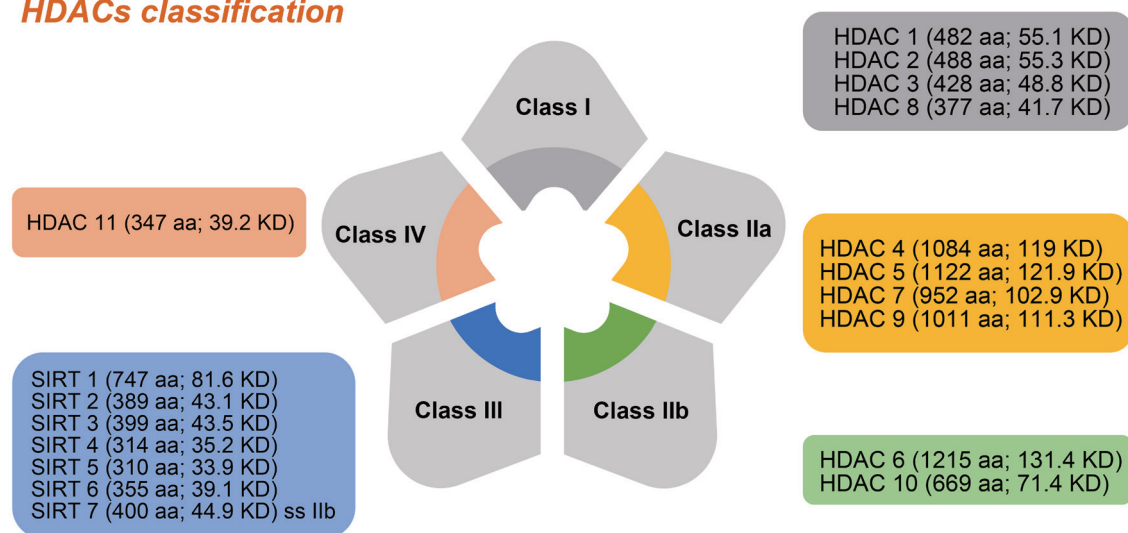


Fig. 1. The different HDACs are classified according to their respective length and molecular weight.^{46,47} aa, amino acid; HDAC, histone deacetylase; KD, kilodalton; SIRT, sirtuin.

in the same study revealed that tumor growth was suppressed by VPA, and apoptosis-related proteins were altered with downregulation of *BCL-2* and upregulation of *BAX*.^{69,70}

Belinostat

Belinostat is a hydroxamic-acid type HDACi used for the treatment of patients with relapsed or refractory PTCL (peripheral T-

cell lymphoma) (Fig. 2). Because of its poor metabolic stability, belinostat showed a limited effect in solid tumors, such as colon cancer. To overcome this limitation, a prodrug (Cubisbel: complexation of belinostat to Cu) was synthesized and tested *in vitro* (in 3 CRC cell lines: Caco-2, SW480, and SW620) and *in vivo*. The results demonstrated that this prodrug reduced colon cancer cell growth via HDAC inhibition and apoptosis induction. Further-

Table 2. HDACs and HATs involved in CRC

HDAC	Cellular localization	Effect of enzyme inhibition	Reference
HDAC 1	Nucleus	Better overall survival	48
HDAC 2	Nucleus	Better overall survival	49
HDAC 3	Nuclear; Cytoplasm	Better differentiation of tumor cells	48,50
HDAC6	Plasma membrane; Cytoskeleton (microtubule); Cytoplasm; Aggresome; Endosome; Nucleus (nucleoplasm) :	Blocks autophagy flux and tumorigenesis of <i>Myc</i> -driven neuroblastoma or <i>KRAS</i> -driven CRC and MM	52
SIRT2	Plasma membrane; Cytoskeleton (centriole, centrosome, microtubule, meiotic spindle, mitotic spindle); Cytoplasm; Mitochondrion; Nucleus (nucleoplasm, chromosome, telomeric region)	Suppresses angiogenesis in CRC	53
SIRT3	Cytoplasm; Mitochondrion and mitochondrial matrix; Nucleus (nucleoplasm)	Inhibits SHMT2-involved serine disorder in CRC proliferation; Promotes colon sensitivity to inflammation and tumorigenesis of CRC	54,55
SIRT6	Cytoplasm; Nucleus (nucleoplasm, nuclear telomeric heterochromatin, nucleolus)	Enhances aerobic glycolysis and <i>MYC</i> -driven tumor growth in CRC and pancreatic cancer	56
HAT-MOF (KAT8)	Nucleus	Downregulation of H4K16ac, by MOF inhibitor DC-M01-7, inhibits proliferation of human CRC cells (HCT116)	57
p300/CBP	Nucleus	Reduction of histone acetylation and inhibition of the transcription of <i>Hsp70</i> proteins vital for the survival of PTEN-/- colorectal cells	58

CBP, CREB-binding protein; CRC, colorectal cancer; HAT, histone acetyltransferase; HDAC, histone deacetylase; KAT8, lysine acetyltransferase 8; MM, multiple myeloma; MOF, metal-organic framework; MYC, myelocytoma; SHMT2, Serine hydroxymethyltransferase 2; SIRT, sirtuin.

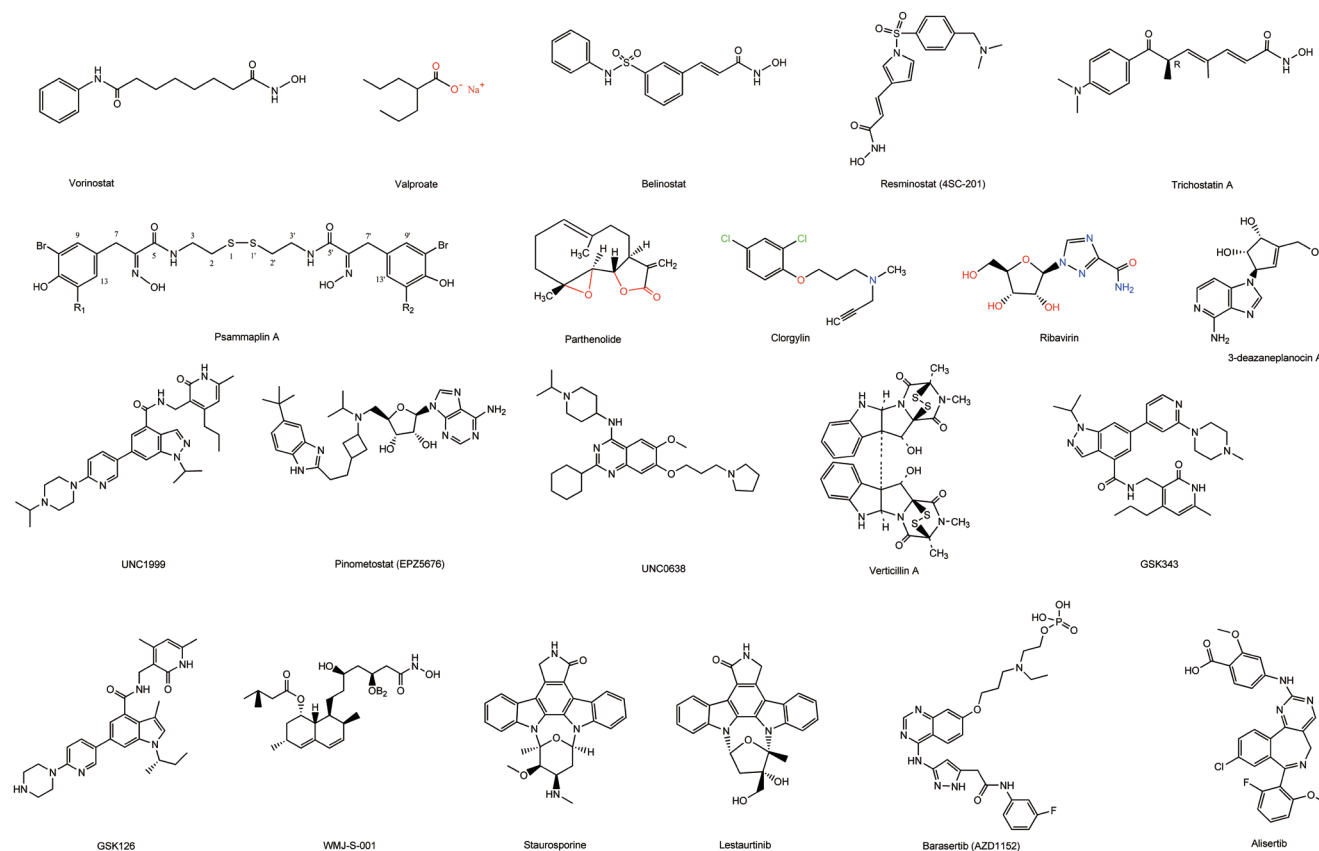


Fig. 2. Chemical structures of some representative HDAC inhibitors in CRC (Vorinostat, Valproate, Belinostat, Resminostat, Trichostatin A, Psammaplin A, Parthenolide, Clorgylin), histone methyltransferase inhibitors in CRC (Ribavirin, 3-deazaneplanocin A, UNC1999, Pinometostat, UNC0638, Verticillin A, GSK343, GSK126), epigenetic modifiers of histone phosphorylation in CRC (WMJ-S-001, Staurosporine, Lestaurtinib, Barasertib, Alistertib). CRC, colorectal cancer; HDAC, histone deacetylase.

more, the treatment of colon cancer PDOs (patient-derived tumor organoids) with Cubisbel led to a significant decrease in cell viability and reduction of stem cell and proliferation markers.⁷¹

Resminostat

Resminostat is an orally bioavailable HDAC inhibitor (Fig. 2). It targets different HDACs of classes I and II, including HDACs 1, 3, 6, and 8. It has been shown that Resminostat has an effect on different types of cancer and is promising because of its tolerability, safety, and the possibility to be used in combination with other drugs like sorafenib and docetaxel.^{72,73} It has been reported that Resminostat can kill cancer cells by affecting the AKT signaling pathway, which can lead to the inhibition of proliferation, migration, and stimulation of apoptosis in CRC cell lines.⁷⁴ Clinical trials are ongoing for advanced CRC, but no results have been published yet.⁷⁵

Psammaplin A (PsA)

PsA is a natural molecule isolated from the *Psammaphysilla sponge* (Fig. 2). This symmetrical bromotyrosine-derived disulfide has various pharmacological activities such as antimicrobial and anti-tumoral.⁷⁶ It has been reported that PsA inhibits enzymes like DNA gyrase, farnesyl protein transferase, DNA topoisomerase, and leucine aminopeptidase.⁷⁶ Additionally, PsA was found to be a potent inhibitor of HDAC, especially Class I HDAC.⁷⁷ This inhibition

is done through the establishment of a coordination link between the zinc ion and the catalytic pocket of HDAC using a sulfhydryl group activated by a reducing agent.⁷⁷

In CRC, it has been shown that PsA could play a key role. In fact, it inhibits cell proliferation and upregulates expression of the TSG *gelsolin* in a dose-dependent manner. Also, this molecule induces H3 and H4 acetylation, increases expression of p21, a cyclin-dependent kinase inhibitor, and decreases expression of *pRb*, cyclins, and CDKs, which promote cell cycle arrest.^{77,78}

Parthenolide

Parthenolide (HDAC1 and DNMT1 inhibitor) is a natural bioactive sesquiterpene lactone (Fig. 2). It is found mostly in the flowers and leaves of the feverfew (*Tanacetum parthenium*) at 0.1–0.2% of its dry weight. It has been shown that Parthenolide inhibits nuclear factor-κB activation by alkylation of Cys38 of the *p65* gene and exhibits anti-tumor effects in human malignancies.⁷⁹ A study reported that this natural bioactive molecule inhibits DNMT1 with an IC₅₀ of 3.5 μM. It acts possibly via alkylation of the proximal thiolate of Cys1226 of the enzyme catalytic domain by its γ-methylene lactone. Furthermore, this molecule downregulates DNMT1 expression. This downregulation may be associated with cell-cycle arrest at SubG1 or the interruption of the binding of a transcription factor Sp1 to the DNMT1 promoter. The same study has shown that Parthenolide leads to the reactivation of the tumor

Table 3. Some epigenetic modifiers of histone acetylation in CRC

Drug	Chemical class	Targeted HDAC/HAT	Status	Selective	Reference
Vorinostat (SAHA)	Hydroxamic acids	HDAC-6	FDA (2006)	Yes	63
Belinostat (PXD101; PX105684)	Hydroxamic acids	HDAC-6	FDA (2014)	No	71
Panobinostat (LBH589)	Hydroxamic acids	HDAC-6	FDA and EMA (2015)	No	96
Resminostat (RAS2410; 4SC-201)	Hydroxamic acids	HDAC-6	Phase II	Yes	74
Quisinostat (JNJ-26481585)	Hydroxamic acids	HDAC-6	Phase I/II	No	97
MPTOE028	Hydroxamic acids	HDAC-6	Phase I	No	98
CUDC 101	Hydroxamic acids	HDAC-6	Phase I	No	99
Fimepinostat (CUDC-907)	Hydroxamic acids	HDAC-6	Phase I	No	100
Rocilinostat/Ricolinostat (ACY1215)	Benzamide	HDAC-6	Phase I/II	Yes	101
Parthenolide	Sesquiterpene lactone	HDAC			80,81
Valproic acid	Fatty acids	HDAC-6	Phase I/II/III/IV	No	69,70
AR-42 (OSU-HDAC42)	Fatty acids	HDAC-6	Phase I	No	102
Pivanex (AN-9) and AN-7	Fatty acids	HDAC-6	Phase II	No	103
EDO-S101 (Tinostamustine)	Other	HDAC-6	Phase I/II	No	104
Nicotinamide	Sirtuins	SIRT5	Phase III		95
DC-M01-7	Sulfonamide	HAT-MOF		unknown	105
Anacardic acid	Salicylic acid	P300/CBP		unknown	106
MHY218	Hydroxamic acids	HDAC1, 4, and 6		Yes	87,107
WMJ-S-001	Hydroxamic acids	HDAC1, 6, and 8		Yes	87,106

CBP, CREB-binding protein; CRC, colorectal cancer; HAT, histone acetyltransferase; HDAC, histone deacetylase; MOF, metal-organic framework; SIRT5, sirtuins.

suppressor *HIN-1* gene *in vitro* associated with its promoter hypomethylation.⁷⁹ Taken together, these results suggest that parthenolide may be an effective anticancer epidrug, in particular against CRC. In fact, it has been reported that parthenolide, as other natural products, inhibits HDAC activity *in silico*, downregulates HIF-1 α , and inhibits the NF- κ B pathway.^{80–82}

Trichostatin A (TSA)

TSA is a natural product isolated from *Streptomyces hygroscopicus* (Fig. 2). It is a hydroxamic acid with important pharmacological activities.⁸³ This molecule is also known as an inhibitor of the canonical HDACs class I and II, which makes it one of the most promising epidrug agents against cancer.⁸³ It has been reported that TSA can make cancer cells more sensitive to radiotherapy. In fact, pre-exposure of head and neck cancer cell lines, HN-3 and HN-9, to 200 nM of TSA for 18 h marked them radiosensitive.⁸⁴

In CRC, Senaei *et al.*⁸⁵ showed that Trichostatin can decrease cell proliferation and promote apoptosis. The same author confirmed that this molecule downregulates expression of DNMT1 and HDAC1, and upregulates *p21*, *p27*, and *p57*. Also, in human colon HCT116 cells, it has been shown that TSA, as an HDAC inhibitor, induces cell cycle arrest via induction of p15 (INK4b) and inhibition of cyclin D-dependent kinases.⁸⁶

Other hydroxamic acid derivatives

Hydroxamate derivatives have been widely explored for their interesting pharmacological activities, particularly against cancer.⁸⁷ It

has been reported by several studies that hydroxamate derivatives could inhibit HDACs. Sixto-López *et al.*⁸⁷ showed that hydroxamic acid derivatives inhibited HDAC 1, HDAC 6, and HDAC 8 with antiproliferative activity. Among these molecules, MHY218 has been reported to induce apoptosis, downregulation of NF- κ B gene expression, G2/M phase arrest, and increase of *p21* (WAF1/CIP1) gene expression level.⁸⁸ Another aliphatic hydroxamate derivative, WMJ-S-001, induced apoptosis in HCT116 cells, and its action was associated with activation of *p38* mitogen-activated protein kinase (MAPK) and AMP-activated protein kinase (AMPK), phosphorylation and acetylation of *p53*, and modulation of proteins such as cyclin D1, *p21* (CIP/WAF1), survivin, and BAX. The same study showed that WMJ-S-001 inhibited the growth of subcutaneous xenografts of HCT116 cells *in vivo*.⁸⁹

Burkholdacs A

Burkholderia is a pathogenic bacterium that has gained increasing interest because of its genome containing a large number of gene clusters encoding for cryptic small molecules that can interact with proteins (Fig. 2). Among those molecules, Burkholdacs A and Burkholdacs B are the most studied because of their interesting activity as HDAC inhibitors.⁹⁰ They target HDAC1 and HDAC6 by inhibiting their catalytic activity through reducing disulfide bonds, which leads to the generation of a free thiol group that interacts with the catalytic site of the enzyme. Tested against six CRC cell lines, Burkholdacs A was reported to have more affinity for HDAC1 and a stronger antiproliferative effect than Burkholdacs B.⁹¹

Table 4. Alterations of histone methylation involved in CRC

Methylation	Fonction	Reference
H3K4me2	Hypermethylation in CRC tissues	110
H3K4me3	Hypomethylation in CRC tissues	21
H3K9me2	Hypermethylation in CRC cell lines and liver metastasis	3
H3K27me2	Hypermethylation in CRC tissues	26
H3K27me3	Hypermethylation in CRC tissues	21
H3K36me2	Hypomethylation in CRC liver metastasis	26
H3K79me2	Hypermethylation in patients with CRC	28
H4K20me2	Hypomethylation in CRC cell lines	16
H4K20me3	Hypomethylation in CRC patients plasma	22

CRC, colorectal cancer; H, histone; me, methylation.

Clorgylin

Clorgylin (hydrochloride) inhibits monoamine oxidase A in a potent, selective, and irreversible way (Fig. 2). It has been demonstrated that this molecule could be a good candidate as an epidrug in CRC.⁹² In fact, clorgylin could restore some silenced TSGs by DNA demethylation of their promoters or by enriching H3K4me2 and H3K4me1 histone marks. Additionally, it has been shown that clorgylin inhibits LSD1 and decreases cancer cell proliferation.⁹²

Nicotinamide

Nicotinamide, a water-soluble form of Vitamin B3, is a precursor of NAD⁺, which makes this molecule a potent inhibitor of enzymes requiring NAD⁺ for their activities (Fig. 2)^{93,94}, such as poly-ADP-ribose polymerases, mono-ADP-ribosyltransferases, CD38, and cyclic ADP ribose/NADase. Furthermore, this molecule has been demonstrated to be an inhibitor of the sirtuin family of HDAC NAD-dependent class III enzymes.^{93,94} Some studies suggest that nicotinamide could play a key role in the prevention and treatment of some cancers such as non-melanoma skin cancer, head and neck cancer, laryngeal cancer, and urinary bladder cancer. In addition, nicotinamide is a safe, well-tolerated, and cost-effective drug.^{93,94}

Gupta *et al.*⁹⁵ showed that nicotinamide could be used as an adjuvant treatment in CRC since, when paired with carbogen, it increased the delivery of anticancer drugs to CRC metastases in patients with advanced cancer.

Other molecules

As summarized in Table 3 with references,^{63,69–71,74,80,81,87,95–107} many other molecules could be used as epigenetic modifiers proposed for the treatment of CRC. These molecules are Panobinostat, Quisinostat, Fimepinostat, Rocilinostat, Pivanex (AN-9), EDO-S101 (Tinostamustine), DC-M01-7, and Anacardic acid.

Role of HDACi in synergistic therapy against cancer

Several combined therapies (HDACi + anticancer drug) have been investigated in clinical trials to treat different types of cancers. Among these associations, (belinostat + Cisplatin) in small cell lung cancer and neuroendocrine cancer,¹⁰⁸ (Entinostat + Trastuzumab (anti-HER2⁺)) in HER2⁺ breast cancer, (HDACis (panobinostat or vorinostat), poly ADP ribose polymerase inhibitors (talazoparib or olaparib) and decitabine) in breast and ovarian cancers,¹⁰⁹ (Panobinostat + Bicalutamide/Casodex (androgen receptor antagonist)) in castration-resistant prostate cancer.¹¹⁰

Against CRC, the association (vorinostat (SAHA, Zolinza) + Hydroxychloroquine (autophagy inhibitor)) has been investigated in advanced renal and CRC in a clinical trial (Clinical Trial registration number: NCT01023737: Phase I (finished)). The result showed safety and preliminary efficacy with the maximum tolerated dose.¹¹¹ Other combinations showed promising results in this sense, such as (PsA + Cladribine) and (HDACi + ribavirin).^{112,113}

Epigenetic modifiers of histone methylation in CRC

Histone methylation

Histone methylation consists of the transfer of a methyl group from S-adenosylmethionine (methyl donor) to the amino acid residues of histones, especially arginine and lysine. This transfer, which is a dynamic event similar to histone acetylation, is carried out by enzymes called histone methyltransferases (see Tables 4 and 5).^{3,16,21,22,26,28,110,114–132} In CRC, methylation predominantly occurs on H3 and H4.¹³³ The extensively studied alterations are summarized in Table 4.^{3,16,21,22,26,28,110}

Histone methyltransferase inhibitors in CRC

Ribavirin

Ribavirin is a synthetic nucleoside analogue (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) used as an antiviral drug against hepatitis C infection in combination with interferon (Fig. 2).¹³⁴ Ribavirin is known as an inhibitor of some enzymes such as eIF4E, inosine 5'-monophosphate dehydrogenase, and histone methyltransferase zeste homolog 2 (EZH2). Its activity as an inhibitor of enzymes involved in epigenetic mechanisms was evaluated in various cancer cell lines including CRC cells. The results showed that ribavirin decreased EZH2 expression, inhibited histone methyltransferase activity, and decreased H3K27me3. It also downregulates eIF4E and inosine 5'-monophosphate dehydrogenase type 1.¹³⁴ Furthermore, Ge *et al.*¹³⁵ showed that ribavirin significantly reduced PRMT5 and eIF4E levels and decreased H3R8me2 and H4R3me2 in CRC cell lines. All these results make this molecule a good candidate to be repositioned as an anticancer epidrug in CRC.

UNC1999

UNC1999 is an orally bioavailable molecule that inhibits EZH2 and EZH1 with IC₅₀ of 2 nM and 45 nM (Fig. 2), respectively, in a potent and selective way on epigenetic and non-epigenetic targets. It has been shown that this promising molecule is a potent autophagy

Table 5. HMTs involved in CRC

Enzyme	Class	Mechanism	Effect on CRC	Refer- ence
EZH2	KMTs (methylation of histone lysines)	Interaction with miR-26	Represses gene expression in digestive cancers via H3K27me	114
		H3K27me3 is enriched in the Kruppel-like factor 2 (KLF2) promoter, leading to the growth and proliferation of GC and CRC cells, via the HIF-1 α /Notch-1 signaling pathway and the Hedgehog pathway	Increases proliferation	115,116
		The proliferation of CRC cells is significantly accelerated by the EZH2-mediated H3K27me3 modification of the dual specificity phosphatase 5 (<i>DUSP-5</i>) gene (a negative regulator of the MAPK-signaling pathway)	Increases proliferation	117,118
		CXCR4 that is promoted by EZH2-mediated loss of miR-622 can facilitate the evasion of immune surveillance by binding to CXCL12	Immune escape	119
		EZH2 is activated by loss of ten-eleven translocation 1 (TET1), and leads to repression of E-cadherin gene transcription by catalyzing H3K27me3 modification in the E-cadherin promoter in CRC cells, which leads to a decrease in the expression of E-cadherin (a hallmark of EMT)	EMT	120,121
DOT1L		Methylation of lysine 79 of histone H3	High expression of <i>DOT1L</i> and its activity predict poor patient survival in CRC	122
KMT2A (MLL1 mixed lineage leukemia 1)	KMTs	KMT2A acts by forming the MWRAD complex with WD repeat domain 5 (WDR5), RBBP5, ASH2L, and DPY30	knockdown of WDR5 impacts H3K4 methylation in CRC cells	123,124
KMT3A	KMTs	Decrease in H3K36me3 due to the absence of KMT3A leads to up-regulation of disheveled segment polarity protein 22 (DVL), which results in the enhancement of Wnt/ β -catenin signaling pathway activity and thereby drives colorectal carcinogenesis	Carcinogenesis	125
KMT2D	KMTs	The loss of H3K4me3 in metabolic pathway genes because of KMT2D inhibition leads to alterations in aerobic glycolysis and lipid levels via GLUT3-mediated processes	Metabolic reprogramming	126
KDM6A (ubiquitously transcribed X (UTX))	KDMs (demethylation of histone lysines)	Targets H3K27 in COMPASS (complex proteins associated with Set1), contributing to transcriptional activation; KDM6A interacts with the histone acetyltransferase protein CBP and recruits it to the CDH1 (E-cadherin) promoter in HCT-116 CRC cells, resulting in increased H3K27ac	EMT	127,128

(continued)

Table 5. (continued)

Enzyme	Class	Mechanism	Effect on CRC	Reference
KDM3A (H3K9me1/2 demethylase)	KDMs	<i>PHF5A</i> acetylation increases the level of KDM3A by reducing its aberrant alternative splicing of its mRNA in CRC, thereby modulating stress responses and carcinogenesis in CRC		
KDM4B	KDMs	The Warburg effect: Glucose transporter 1 (GLUT1) can be activated by p-ERK/KDM4B-mediated removal of the repressive H3K9me3 mark, which results in glucose uptake in CRC cells under glucose deprivation conditions	Metabolic reprogramming	129
PRMT6	PRMTs (Protein Arginine Methyltransferases): Catalyze Histone arginine methylation	In CRC, PPAR α (intestinal-specific peroxisome proliferator-activated receptor α) deficiency promotes PRMT6 expression via the RB1/E2F pathway, which enhances the enrichment of H3R2 asymmetric dimethylation (H3R2me2a) in the promoter of p27		130
PRMT1	PRMTs	Coactivator of hormone receptor function; Essential component of the MLL oncogenic transcriptional complex	Aberrant expression in CRC	131
PRMT5	PRMTs	Reduced H3K4me3 and repressive H3K27me3 marks are significantly enriched in the PRMT5 gene promoter in HCT116 cells with depletion of NAA40 (N-alpha-acetyltransferase 40)		132

CRC, colorectal cancer; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DOT1L, disruptor of telomeric silencing 1-like; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homologue 2; GC, gastric cancer; GLUT3, glucose transporter type 3; H, histone; HIF-1 α , hypoxia-inducible factor-1- α ; HMT, histone methyltransferase; KDM, histone demethylase; KMT, lysine methyltransferase; MAPK, mitogen-activated protein kinase; me, methylation; miR, microRNA; MLL, mixed lineage leukaemia; mRNA, messenger RNA; PPAR α , peroxisome proliferator-activated receptor α ; PRMT, protein arginine methyltransferase; TET, ten-eleven translocation; WDR5, WD repeat domain 5; WRAD, WD repeat containing protein 5 (WDR5); Retinoblastoma binding protein 5 (RbBP5); Absent-Small-homeotic-2-like protein (ASH2L), and Dumpy-30 (Dpy30).

inducer and has important antiproliferation, differentiation, and apoptosis effects on leukemia cells. The study of its epigenetic activity showed that it specifically suppresses H3K27me3/2.¹³⁶ In a study by Lima-Fernandes *et al.*,¹³⁷ it has been reported that inhibition of H3K27 methylation by EZH2 leads to increased sensitivity of CRC cell lines to 5-FU. This inhibition was accompanied by downregulation of H3K27me3 in Indian Hedgehog and decreased self-renewal of CRC-initiating cells.¹³⁷

Pinometostat (EPZ5676)

Pinometostat (or EPZ5676) inhibits the histone methyltransferase DOT1L with a K_i of 80 pM (Fig. 2). It acts as an S-adenosyl-methionine-competitive inhibitor. This molecule also inhibits the histone methyltransferases EZH2, KMT-4, and KDM1A. Other studies showed that the combination of pinometostat with 5-FU and poly ADP ribose polymerase inhibitors, which are used in the treatment of CRC, has an additive effect accompanied by a decrease in H3K79me3 levels.¹³⁸ This result is supported by Phase I clinical trials that showed an inhibitory effect of H3K79 methylation in cancer by pinometostat.¹³⁹

UNC0638

UNC0638 has a strong and selective inhibitory effect on G9a and GLP histone methyltransferases (Fig. 2), with IC₅₀ values of <15 nM and 19 nM, respectively. It also has antiviral activities.¹⁴⁰ In CRC, this molecule increased the cytotoxic activity of topoisomerase-based treatment with a decrease in H3K9me2 in the PP2A promoter, which activates the PP2A-RPA axis.¹⁴¹

Verticillin A

Verticillins are epipolythiodioxopiperazine alkaloids (Fig. 2). Some molecules of this class exhibit strong cytotoxic effects against various cancer cell lines.¹⁴² Regarding its epigenetic modifier activity in CRC, it has been reported that Verticillin A selectively inhibits many histone methyltransferases such as SUV39H1, SUV39H2, G9a, GLP, NSD2, and KMT2A.¹⁴³ This effect leads to a decrease in the level of trimethylation of lysine 9 on H3 in the *FAS* promoter, which restores its expression. All of this results in alleviating 5-FU resistance in CRC. Furthermore, Verticillin A is less toxic and more efficient than other epigenetic modifiers like decitabine and vorinostat.¹⁴³

GSK343

GSK343 can inhibit EZH2 in a potent and selective manner more effectively than other histone methyltransferases (Fig. 2). It showed an IC₅₀ of 4 nM in a cell-free assay (60-fold selectivity against EZH1 and >1000-fold selectivity against others).¹⁴⁴ A recent study found that the inhibitory effect of GSK343 on EZH2 is accompanied by a gradual decrease in H3K27me3, amelioration of intestinal inflammation, and delayed colitis-associated cancer onset.^{145,146}

3-deazaneplanocin A

3-deazaneplanocin A is an adenine analog that inhibits, as a competitive inhibitor (Fig. 2), S-adenosylhomocysteine hydrolase with a K_i of 50 pM, which modulates chromatin accessibility by inhibiting histone methyltransferases such as EZH2.¹⁴² This effect significantly reduces H3K27me3 levels and leads to a notable decrease in cell proliferation and migration in CRC.¹⁴⁷

GSK126

GSK126 is a promising molecule since it can inhibit the EZH2 histone methyltransferase in a potent and selective way, with an

IC₅₀ of 9.9 nM (Fig. 2).¹⁴⁸ Huang *et al.*¹⁴⁹ found that the effect of GSK126 on EZH2 suppressed EZH2-mediated H3K27me₃, which results in an increase in myeloid-derived suppressor cells and a decrease in CD4⁺ and IFN- γ ⁺ CD8⁺ T-cell levels, both of which are strongly involved in antitumor immunity in CRC.¹⁴⁹

Epigenetic modifiers of Histone phosphorylation

Alteration of Phosphorylation in CRC

It has been shown that H3S10ph can play an important role in the regulation of gene transcription. In fact, this epigenetic modification leads, during interphase, to chromatin relaxation and gene expression, whereas it inhibits gene expression during mitosis by chromatin condensation. Several kinases can be responsible for H3Ser10 phosphorylation, such as RSK2, MSK1/2, PKA, Aurora kinase, Nima kinase, and IKK- α .¹⁵⁰ One of these kinase pathways, Aurora kinase, has been reported to be associated with CRC.¹⁵¹ In fact, several studies have shown that Aurora B, which initiates H3S10ph, is overexpressed in CRC, breast cancer, and various other cancers.¹⁵² Li *et al.*¹⁵³ reported that AURKB is highly expressed and positively correlated with *Ki-67* expression in CRC, promoting the growth of CRC cells and xenograft tumors *in vivo*.

H2A is another histone phosphorylation that was found to correlate with mitotic chromatin condensation. The mammalian variant of this phosphorylated histone, H2AX, is phosphorylated at Ser139 when exposed to mutagenic agents.¹⁵⁴ Also, the mRNA level of H2AX has been reported to be elevated in CRC tissues compared to normal tissues.¹⁵⁴

Other phosphorylations of different histone sites have been reported to play key roles in carcinogenic pathways through mediating DNA damage response. These include tyrosine phosphorylation of core histones, such as phosphorylation of H2A.X at Tyrosine 142^{155,156} and phosphorylation of H3 at Tyrosine 41.¹⁵⁷ Additional modifications include H3S10ph, Threonine 11, and Serine 28; phosphorylation of H4 at Serine 1 and Tyrosine 51; phosphorylation of H2B at Threonine 129; and phosphorylation of linker histone H1, subtype H1.2, at Threonine 145.¹⁵⁷ These post-translational modifications are regulated by specific protein kinases like PKA, CDK, and ATR, and phosphatases such as PP2A.¹⁵⁸

Among these histone phosphorylations, the phosphorylation of H2A.X at Tyrosine 142 has been shown to be involved in CRC. In fact, Ge *et al.*¹⁵⁹ reported that Livin (an inhibitor of apoptosis protein) promotes autophagy in HCT116 and SW480 cells (CRC cells) via regulation of the phosphorylation of H2A.XY 142.

All these data suggest the involvement of phosphorylation in chromatin alteration, DNA repair, and genome integrity. Additionally, it has been reported that *H2AX* plays an important role in cancer as a TSG.¹⁵⁴ Therefore, targeting kinases and phosphatases responsible for the alteration of histone phosphorylation by natural or synthetic molecules is another promising approach to explore for developing epigenetic modifiers to treat cancer, CRC in particular.

Epigenetic modifiers of histone phosphorylation in CRC

WMJ-S-001 (hydroxamic acid derivative)

Besides their important effect as HDAC inhibitors, as mentioned previously in this article, hydroxamate derivatives can also play a role in histone phosphorylation. In fact, a study by Huang *et al.*¹⁶⁰ reported that WMJ-S-001, a novel aliphatic hydroxamate derivative, inhibited proliferation and induced apoptosis in HCT116 (CRC cell line) (Fig. 2). This effect was associated with *p53* phosphorylation and acetylation, among other effects such as AMPK

and *p38* MAPK activation. On the other hand, it has been shown that WMJ-S-001-induced *p53* phosphorylation was reduced by AMPK-*p38*MAPK signaling blockade. Furthermore, the effect of WMJ-S-001 was confirmed by an *in vivo* test that showed that this molecule suppresses the growth of subcutaneous xenografts of HCT116 cells.^{160,161}

Barasertib (AZD1152)

AURKB knockdown inhibited CRC proliferation and triggered cell cycle arrest in the G2/M phase, which could be an interesting target in CRC treatment. In fact, inhibition of AURKB with a specific inhibitor called barasertib (or AZD1152) suppressed cyclin E1 expression in CRC cells and inhibited tumor cell growth (Fig. 2).¹⁶² AZD1152 is a dihydrogen phosphate prodrug of a pyrazoloquinazoline that is rapidly converted to the active form, AZD1152-HQPA, in plasma. Barasertib is highly potent (*K_i* = 0.36 nmol/L), and its inhibition effect on human CRC growth ranges from 55% to $\geq 100\%$ (*P* < 0.05) in immunodeficient mice.¹⁶³ Furthermore, a study by Shah *et al.*¹⁶⁴ showed that AZD1152 increases the sensitivity of CRC cells to 5-FU.

Staurosporine

The role of H1 and H3 phosphorylation in controlling chromosome condensation was studied in the mouse FM3A cell line, and it was shown that these histone phosphorylations correlated with G2 to M condensation of chromosomes.¹⁶⁵ The same study reported that staurosporine, a natural product isolated from *Streptomyces staurosporeus*, could inhibit the protein kinase responsible for this phosphorylation during mitosis, which prevents cells from entering mitosis (Fig. 2). Furthermore, when added to cells arrested at metaphase, staurosporine causes H1 and H3 dephosphorylation, which leads to the decondensation of chromosomes.¹⁶⁵ Another study reported that staurosporine induces apoptosis in CRC cells.¹⁶⁶

Lestaurtinib

Lestaurtinib is a semisynthetic derivative of indolocarbazole K252a, structurally related to staurosporine (Fig. 2). It is a potent inhibitor of kinases such as PRK1 *in vitro* and *in vivo* (among others). It has been studied for the treatment of various cancers.¹⁶⁷ It was shown that Lestaurtinib inhibits H3 threonine phosphorylation in cell culture.¹⁶⁸

Alisertib

Alisertib (MLN 8237) is a molecule that inhibits Aurora A kinase in a selective way (IC₅₀ = 1.2 nM), inducing apoptosis and autophagy through targeting the AKT/mTOR/AMPK/*p38* pathway (Fig. 2).¹⁶⁹ Tested in a panel of CRC cell lines expressing different *KRAS* alleles, including Caco-2 (*KRAS* WT), Colo-678 (*KRAS* G12D), SK-CO-1 (*KRAS* G12V), HCT116 (*KRAS* G13D), CCCL-18 (*KRAS* A146T), and HT29 (BRAF V600E), it has been shown that this molecule can modulate the active form of *KRAS*. The same study reported that the effect of Alisertib, which acts via the PI3K/Akt and MAPK pathways, was increased when combined with the MEK inhibitor Selumetinib.¹⁷⁰

Limitations and future challenges

Limitations

Epidrugs, or epigenetic modifiers, are emerging as a new class of molecules targeting epigenetic alterations involved in cancer onset

and progression. These epigenetic modifiers are promising because of their capability to restore the normal function of oncogenes and TSGs in different types of cancer, including CRC. However, like any other drug, they present some limitations that researchers need to overcome. One of these limitations is their adverse effects. In fact, these molecules target enzymes responsible for epigenetic mechanisms such as DNMT, HDAC, EZH2, etc., that ensure several physiological processes necessary for the proper functioning of the body. Also, these molecules could inhibit other enzymes, which could lead to off-target effects. Another gap in this field is that studies are primarily focused on DNA methylation, histone acetylation, and methylation. Other histone modifications, such as phosphorylation, ubiquitination, neddylation, ADP-ribosylation, and sumoylation, are less explored. Additionally, epigenetic-targeted drugs face other challenges such as clinical efficacy, toxicity, lack of selectivity, and resistance.¹⁷¹

To overcome all these limitations and gaps, research on epigenetic modifiers has progressed in recent years. In fact, many strategies are under exploration, especially combination therapies and epigenetic degraders.

Future challenges

Combinations

Combining epidrugs with each other or with other anticancer treatments such as conventional chemotherapy, immunotherapy, precision medicine, or radiotherapy is the most explored strategy in cancer treatment. Since histone modifications interact with each other, molecules targeting different histone alterations could be combined. In this context, vorinostat and Panobinostat (HDAC inhibitors) and BET inhibitors were investigated in association with kinase inhibitors to increase their anticancer activity.¹⁷² Alisertib combined with Fulvestrant showed an interesting clinical effect in patients with breast cancer.¹⁷³

As a therapeutic strategy against cancer, the combination has two benefits: modulating the characteristics (metabolic and pathological) of cancer cells, immune cells, and stromal cells in the TME,¹⁷⁴ and avoiding drug resistance that could be caused by epigenetic alterations.¹⁷⁵ Development of dual inhibitors, like CUDC907, CUDC101, and 4SC-202, is also considered a promising strategy to overcome drug resistance, particularly in kinase-driven cancers.¹⁷⁶

Epigenetic degraders

Epigenetic degraders are a novel class of epigenetic-targeted drugs developed to overcome the limitations of traditional epidrugs such as enzyme inhibitors. These new epigenetic modulators, which include PROTACs (proteolysis-targeting chimeras), molecular glues, and hydrophobic tagging, are increasingly being explored, and several epigenetic degraders have been developed in the past five years. Conventional epigenetic modulators (e.g., inhibitors/agonists) must bind to the active site of their protein targets because they act by either inhibiting or enhancing target protein activity. However, the problem is that drug targets have shown that only about 20% of them have a targetable active site, which makes the remaining 80% undruggable.¹⁷⁷

About 20 PROTAC degraders have been developed in recent years and are undergoing clinical trials. However, only a few of them are epigenetic degraders, such as CFT8634, FHD-609, and RNK05047, for late-stage synovial sarcoma patients.¹⁷⁸ These epigenetic PROTACs can target epigenetic readers (e.g., dBET1 for BET degradation),¹⁷⁹ epigenetic writers (e.g., MS1943 for EZH2

degradation),¹⁸⁰ or epigenetic erasers (e.g., NP8 for HDAC6 degradation).¹⁸¹

Regarding CRC, it has been shown by Zaman *et al.*¹⁸² that synthesized cereblon-recruiting PROTACs were able to eliminate CRC stem cells through inhibition of Wnt/ β -catenin signaling by degrading KDM3A and KDM3B in a selective way.

As for other epigenetic degraders, Moon *et al.*¹⁸³ reported the efficacy of IL6-54 and IL6-110 as molecular glues selectively inhibiting CDK12/13 in breast and gastric cancer. As a hydrophobic tagging degrader, Fulvestrant has been reported to have anti-CRC activity.¹⁸⁴

Other future challenges

Researchers are increasingly interested in other strategies as future challenges, such as hybrid molecules derived from HDAC inhibitors, targeted delivery systems, and multitarget agents.^{185,186}

Conclusions

Targeting epigenetic alterations is a promising strategy to treat cancer, CRC in particular, explored by an increasing number of studies. In this context, many natural and synthetic molecules have been tested, particularly against CRC cell lines. By correcting alterations in histone acetylation, methylation, and phosphorylation, the normal function of genes controlling pathways involved in CRC could be restored. Some of these molecules, which could be used alone or in combination to improve the efficacy of other anticancer drugs or radiotherapy, are now the subject of ongoing clinical trials. In a future article, we aim to explore epigenetic modifiers that could correct other histone modifications such as sumoylation, ADP-ribosylation, neddylation, and ubiquitination. Also, combinations and quantitative structure-activity relationships of different epigenetic modifiers will be analyzed to identify the most efficacy way to use them.

Acknowledgments

The author acknowledges Mohamed Amine Jaafari for his help in revising the English.

Funding

No funding was provided to support this publication.

Conflict of interest

The author declares no conflict of interest related to this publication.

Author contributions

AJ is the sole author of the manuscript.

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