Modulating epigenetic modifications for cancer therapy (Review)

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Abstract. Cancer is a global public health concern. Alterations in epigenetic processes are among the earliest genomic aberrations occurring during cancer development and are closely related to progression. Unlike genetic mutations, aberrations in epigenetic processes are reversible, which opens the possibility for novel pharmacological treatments. Non-coding RNAs (ncRNAs) represent an essential epigenetic mechanism, and emerging evidence links ncRNAs to carcinogenesis. Epigenetic drugs (epidrugs) are a group of promising target therapies for cancer treatment acting as coadjuvants to reverse drug resistance in cancer. The present review describes central epigenetic aberrations during malignant transformation and explains how epidrugs target DNA methylation, histone modifications and ncRNAs. Furthermore, clinical trials focused on evaluating the effect of these epidrugs alone or in combination with other anticancer therapies and other ncRNA-based therapies are discussed. The use of epidrugs promises to be an effective tool for reversing drug resistance in some patients with cancer.

Contents

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1. Introduction

Cancer is one of the leading cause of death worldwide; according to estimates from the World Health Organization, ~10 million cancer deaths occurred in 2020 (1). Cancer results from DNA aberrations that cause the deregulation of pathways controlling cellular processes involved in proliferation, cell survival, apoptosis and DNA repair. Mutations in tumor suppressor genes and oncogenes are responsible for cancer initiation, promotion and progression (2). However, carcinogenesis cannot be explained solely by genetic alterations, as it also involves epigenetic processes. Epigenetic changes are defined as inheritable modifications in gene expression that do not result from changes in DNA sequences (3). Epigenetic mechanisms were discovered as the knowledge regarding DNA structure increased. DNA is packaged in the nucleus by histones into a structure called chromatin. The basic unit of chromatin is the nucleosome; each nucleosome comprises one histone octamer composed of H3, H4, H2A and H2B subunits, with 147 bp of DNA coiling around them. Chromatin is classified as either heterochromatin or euchromatin. Heterochromatin is a region of DNA that is highly condensed and transcriptionally inactive, whereas euchromatin is less condensed and is actively transcribed (4). The chromatin structure creates a barrier to DNA replication, damage repair or access of transcription machinery to DNA. Chromatin is highly dynamic to allow different regulators or transcriptional factors to access DNA (5). Various epigenetic mechanisms regulate the states of euchromatin or heterochromatin. Six epigenetic mechanisms altering chromatin structure have been described (Fig. 1): i) Nuclear dynamic; ii) DNA methylation; iii) covalent histone modification; iv) ATP-dependent chromatin remodeling complexes; v) histone variants; and vi) non-coding RNA (ncRNA), including microRNA (miRNA/miR) and long ncRNA (lncRNA) (5-7).

A number of studies have demonstrated that dysregulation of epigenetic mechanisms is a critical contributor to carcinogenesis (8-10) (Fig. 2), mainly due to regulation of DNA accessibility and the compactness of chromatin structure, favoring the regulation of different genes necessary for carcinogenesis (Fig. 2A and B).

Unlike genetic mutations, the cancer epigenomic landscape can be reprogrammed. It represents one of the most promising therapeutic targets for treatment and reversal of drug resistance. Epigenetic alterations in cancer development and progression may be the basis for individual variations in drug response (11,12). The present review focuses on epigenetic reprogramming during tumorigenesis and recent progress in developing clinical strategies to target epigenetic codes.

2. Epigenetic mechanisms in cancer, roles in carcinogenesis and therapeutic approaches

DNA methylation in cancer. DNA methylation is the most well-studied epigenetic modification. It is a stable gene-silencing mechanism that regulates gene expression and chromatin architecture through the covalent addition of a methyl group to the C5 cytosines by DNA methyltransferases (DNMTs), producing 5-methylcytosine (5mC) (Fig. 1) (12). A total of five members of the DNMT family have been identified in mammals: DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3-like (DNMT3L) (12). However, only DNMT1, DNMT3A and DNMT3B exhibit catalytic activity for DNA methylation (13). The *de novo* methyltransferases DNMT3A and DNMT3B establish DNA methylation during embryonic development (14,15), whereas DNMT1 is a housekeeping methyltransferase that methylates preexisting hemi-methylated DNA and preserves DNA methylation during DNA replication (14). DNMT3L has sequence homology with DNMT3A/3B but has no catalytic domain; however, it is an essential accessory protein for *de novo* methylation (16). Although the mechanism remains unclear, DNMT3L modulates the activity of other DNMTs, including DNMT3A (17) and DNMT2, which act as RNA methyltransferases (18).

DNA methylation is reversible and is mediated by three members of the ten-eleven translocation (TET) family: TET1, TET2 and TET3 (19). TET enzymes function in the demethylation of 5mC to 5-hydroxymethylcytosine (5hmC), which is converted to unmethylated cytosine through sequential oxidation to produce 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) intermediates (20). 5fC and 5caC are subsequently removed by DNA glycosylases and the base excision repair machinery to generate unmethylated cytosines at TET-targeted sites, or they are passively demethylated by the loss of 5hmC during cell division (20). Therefore, TET enzymes regulate the chromatin structure and gene expression (21).

DNA methylation serves a fundamental role in different processes, including embryonic development (22), X chromosome inactivation (23), genomic imprinting (24) and transcriptional silencing (25). CpG islands are often methylated in genome sequences rich in cytosine-guanine nucleotide pairs in normal tissues (16). By contrast, promoter regions are generally unmethylated, except for the inactive X chromosome, silenced alleles of imprinted genes and tissue-specific genes (21). DNA methylation can also be detected in repetitive sequences, either in tandem (satellite DNA), or short- or long-interspersed nuclear elements; these modifications mainly help maintain genomic integrity (26).

Approximately 60% of all gene promoters are enriched in CpG islands; therefore, these genes are potentially epigenetically regulated (26). In cancer cells, alterations in DNA methylation are the first epigenetic marker associated with cancer development (Fig. 2B) (27). Cancer cell genomes are hypomethylated relative to normal counterparts, whereas a paradoxical increment of site-specific CpG methylation is observed in the gene promoter regions (28). Loss of methylation in repetitive regions of the genome is the main cause of DNA hypomethylation (29). It is associated with genomic instability, changes in gene imprinting and increased cancer risk (30). In addition, DNA methylation is substantially more frequent than gene inactivation by genetic mutations (31). It can induce gene silencing directly or indirectly by inhibiting the binding of specific transcription factors or by recruiting methyl-CpG-binding domain proteins, respectively (27). The most crucial tumor-suppressor gene silencing occurs through epigenetic mechanisms (32). This includes p14, p16/inhibitors of CDK4 (33), retinoblastoma, cyclin-dependent kinase inhibitor 2 and methylguanine-DNA-methyltransferase, which favor uncontrolled cellular proliferation (34). In addition, alterations in DNA methylation patterns detected in hematological malignancies are frequently associated with the aberrant activity of enzymes regulating DNA methylation, such as DNMT3A (35).

Alterations in the epigenome and deregulated epigenetic mechanisms cannot entirely explain the process of multistage carcinogenesis. However, epigenetic changes are generally of a clonal nature, and occur in the early generation of cancer cells; this initiates genetic instability resulting in the acquisition of genetic mutations in tumor suppressor genes and the activation of genetic mutations in oncogenes that facilitate cell transformation (28). In addition, epigenetic alterations can lead to the development of drug-resistant phenotypes (Fig. 2). Epigenetic inactivation can directly determine tumor chemosensitivity and influence drug resistance and post-therapy clinical outcomes (36-38). These findings and the reversible nature of the underlying changes have made epigenetic alterations potential rational targets for therapeutic approaches. Classes of chromatin-modifying drugs have been approved by the US Food and Drug Administration (FDA), including two main DNMT inhibitors (DNMTi) and histone deacetylase (HDAC) inhibitors (HDACi; Fig. 3A) (39). Their application can reactivate tumor suppressor genes and synergistically suppress the proliferation of cancer cell lines *in vitro* and *in vivo* (40,41). In addition, DNMTi are involved in responses to radiotherapy and chemotherapy treatment, sensitizing several chemo- and/or radiation-resistant cancer types in the clinical setting (Fig. 3D) (42,43). For example, treatment with 5-Aza-2'-deoxycytidine (5-aza-D) has been shown to be effective in reversing cisplatin resistance in bladder cancer cells, which is mainly associated with promoter demethylation of the HOXA9 gene (44).

DNMTi for cancer treatment. Drugs that inhibit DNA cytosine methylation are divided into two groups: i) Nucleoside

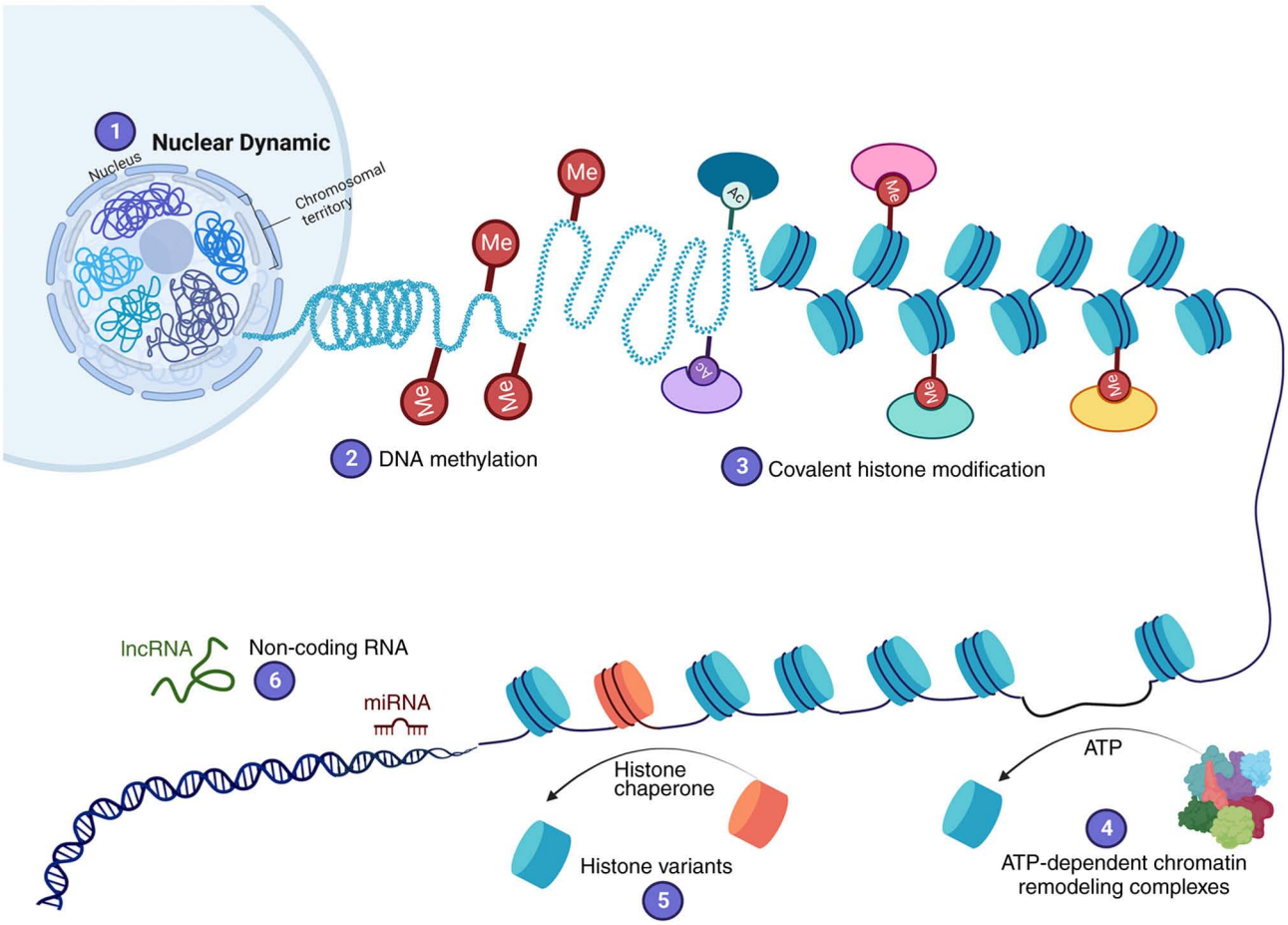

Figure 1. Six epigenetic mechanisms involved in the regulation of gene expression. (1) Nuclear dynamics: The structural and three-dimensional organization of the genome in the nucleus, and short- and long-range interconnected transcriptional regulation, which impacts gene expression. (2) DNA methylation: The addition of a methyl group to cytosine nucleotides by DNA methyltransferases, which induces transcriptional repression. (3) Covalent histone modification: The addition of chemical groups to the amino terminus of histones, which can increase or decrease DNA compaction. (4) ATP-dependent chromatin remodeling complexes: Insertion, removal and displacement of nucleosomes along the DNA through ATP hydrolysis to regulate DNA accessibility. (5) Histone variants: Histone chaperones exchange canonical histones for histone variants (H2A.Z, H2A.X, H3.3 and CENP-A). (6) Non-coding RNA: Non-coding RNA expression promotes transcriptional silencing. Overall, this enables chromatin structure modification to regulate gene expression. Ac, acetyl group; lncRNA, long non-coding RNA; Me, methyl group; miRNA, microRNA.

analogs, including 5-azacytidine (5-aza-C; Vidaza) and 5-aza-D (Dacogen® or decitabine) and zebularine (Fig. 3A) (45); and ii) non-nucleoside drugs, including procainamide, hydralazine, epigallocatechin-3-gallate (EGCG), N-phthalyl-L-tryptophan and MG98 (43,46). Nucleoside analogs are characterized by different modifications of the cytosine ring, such as replacement of carbon with nitrogen at position 5 of the pyrimidine ring (Fig. 4) (47). Cellular uptake of nucleotide analogs is dependent on human equilibrative nucleoside transporter (hENT)-1 and hENT2 (48). Following absorption, they are successively phosphorylated by intracellular deoxycytidine kinase to produce the active tri-phosphorylated metabolite 5-aza-2'-deoxycytidine 5'-triphosphate (49). This subsequently contributes to the loss of methylation through its incorporation into newly synthesized DNA and covalent bond formation with DNMTs (50). Thus, the enzyme remains bound to DNA and its methyltransferase function is blocked (51). Furthermore, the covalent bond compromises DNA functionality by triggering DNA damage signaling, leading to the degradation of these enzymes and the passive demethylation of the cellular genome during DNA replication (45). 5-aza-C and 5-aza-D are the most studied demethylating agents commonly used as chemotherapeutic agents that produce numerous biological effects (Table I) (52,53).

5-aza-C. 5-aza-C was first synthesized in 1960 for use as a classical cytostatic agent and was later shown to inhibit DNA methylation in human cell lines (54-56). It is the first epigenetic drug (epidrug) proposed for use in cancer therapeutics, specifically in patients with acute myelodysplastic syndrome (MDS). In May 2004, the US FDA approved it as a first line treatment for MDS (57). It is also used to treat other hematological malignancies, such as chronic myeloid leukemia (58).

As 5-aza-C contains a ribose in its structure (Fig. 4), it can be incorporated into RNA and DNA (59). There are two main mechanisms of action for 5-aza-C. The first mechanism of epigenetic effects is attributed to its incorporation into DNA, where it induces DNA hypomethylation after several rounds of replication and DNA damage due to adduct formation; therefore, it has been hypothesized that 5-aza-C leads to the activation of repressed tumor suppressor genes (60). On the other hand, most of 5-aza-C (80-90%) is incorporated into RNA (60), which can modify the synthesis of certain proteins

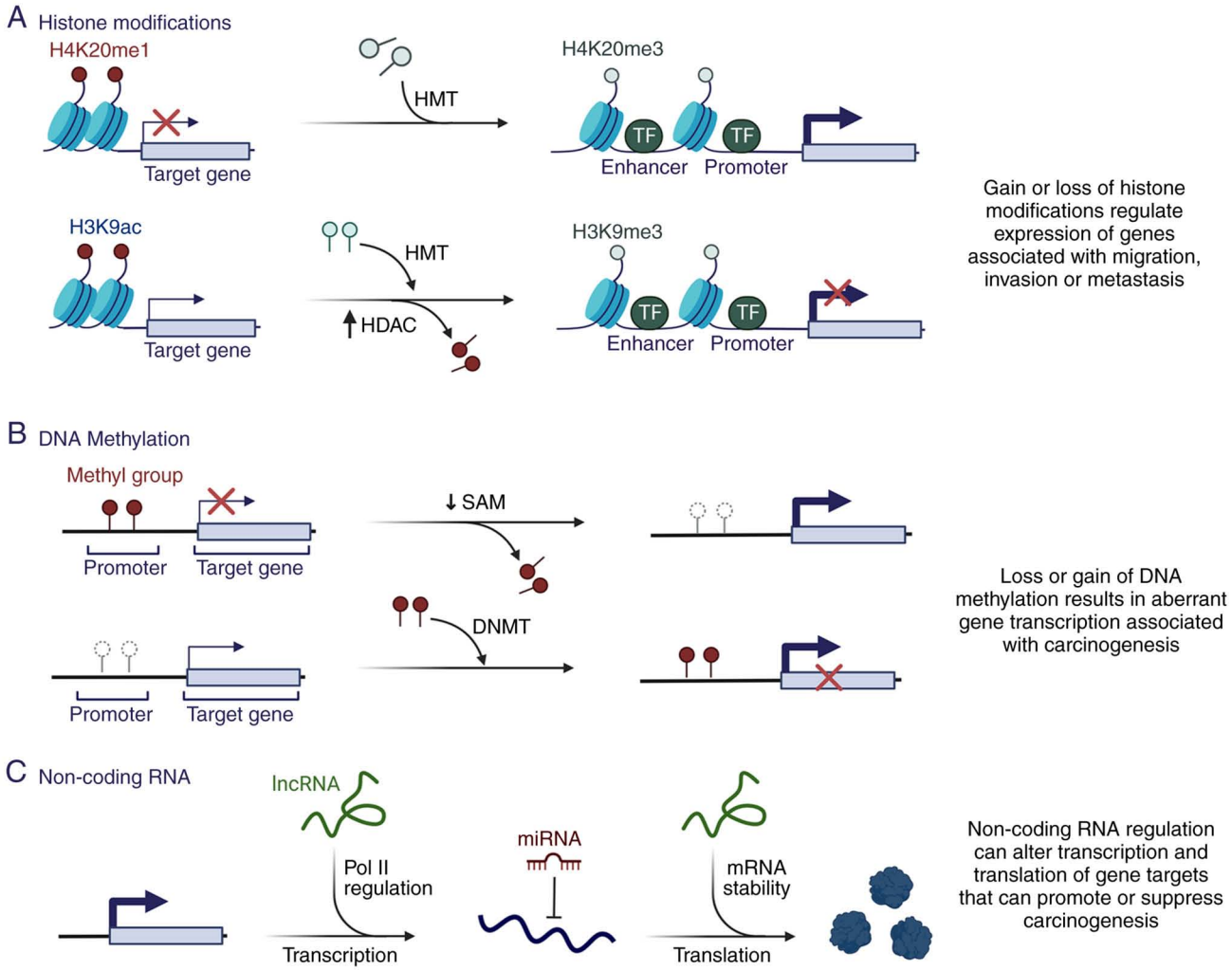

Figure 2. Epigenetic alterations and their contribution to carcinogenesis. (A) Loss or gain of different histone modifications can induce aberrant gene expression and promote carcinogenesis in different tumors. The gain of H3K4me3 by HMT and the loss of H3K9ac by HDAC contributes to the expression of genes associated with carcinogenesis. (B) Alterations in the pattern of DNA methylation and the expression of enzymes, such as DNMTs, are found in several tumors. DNA hypomethylation in various regions increases genomic instability and activates proto-oncogenes, whereas DNA hypermethylation favors the silencing of genes, such as tumor suppressors, which contributes to carcinogenesis. (C) Changes in non-coding RNA expression patterns serve an important role in regulating the initiation and progression of various tumors because they can inhibit or increase gene expression through binding to various target genes. Ac, acetylation; DNMT, DNA methyltransferase; H, histone; HDAC, histone deacetylase; K, lysine; HMT, histone methyltransferase; lncRNA, long non-coding RNA; me1, monomethylation; me3, trimethylation; miRNA, microRNA; Pol II, RNA polymerase II; SAM, S-adenosyl methionine; TF, transcription factor.

by altering the activity of posttranscriptional mechanisms and inducing apoptosis (61-63). Its mechanism of action is concentration-dependent, with high concentrations regulating gene transcription, whereas lower doses induce hypomethylation and inhibit DNMTs (61). Although the main mechanism associated with clinical response observed in patients treated with 5-aza-C remains controversial, the rationale behind the currently approved low-dose therapy for MDS is based on the theory that the induction of hypomethylation with subsequent re-expression of methylated genes will modify gene expression patterns and lead to cell differentiation, apoptosis or senescence of the malignant clone (63).

In preclinical studies, 5-aza-C inhibited the antiapoptotic transcription factor NimA related kinase by decreasing the phosphorylation of the upstream regulator IKKα/β, which induces upregulation of the proapoptotic protein phorbol-12-myristate-13-acetate-induced protein 1, resulting in increased cell death (64,65). Furthermore, 5-aza-C has been proposed to inhibit Wnt signaling, a pathway involved in oncogene expression in acute myeloid leukemia (AML) and other cancer types, such as colon cancer (66,67).

5-aza-D. 5-aza-D is a potent DNMTi included in the group of analogs of the nucleoside cytidine. Because it contains a deoxyribose, it can be incorporated into DNA (Fig. 4) (59,62), unlike 5-aza-C, which predominantly incorporates into RNA (Table I). 5-aza-D covalently binds to DNA during the S-phase of the cell cycle leading to rapid loss of methylated cytosine (66). In 2006, the FDA approved its use in MDS, and it is currently used to treat chronic myelomonocytic leukemia and AML (68).

5-aza-D has direct and indirect effects on gene expression (52). The effect is direct when its incorporation into DNA alters its methylation (69). This is more evident at low concentrations, in which the formation of 5-aza-D/DNMT complexes is limited and does not prevent DNA synthesis (51). High concentrations lead to growth arrest and cell death through increased adduct formation

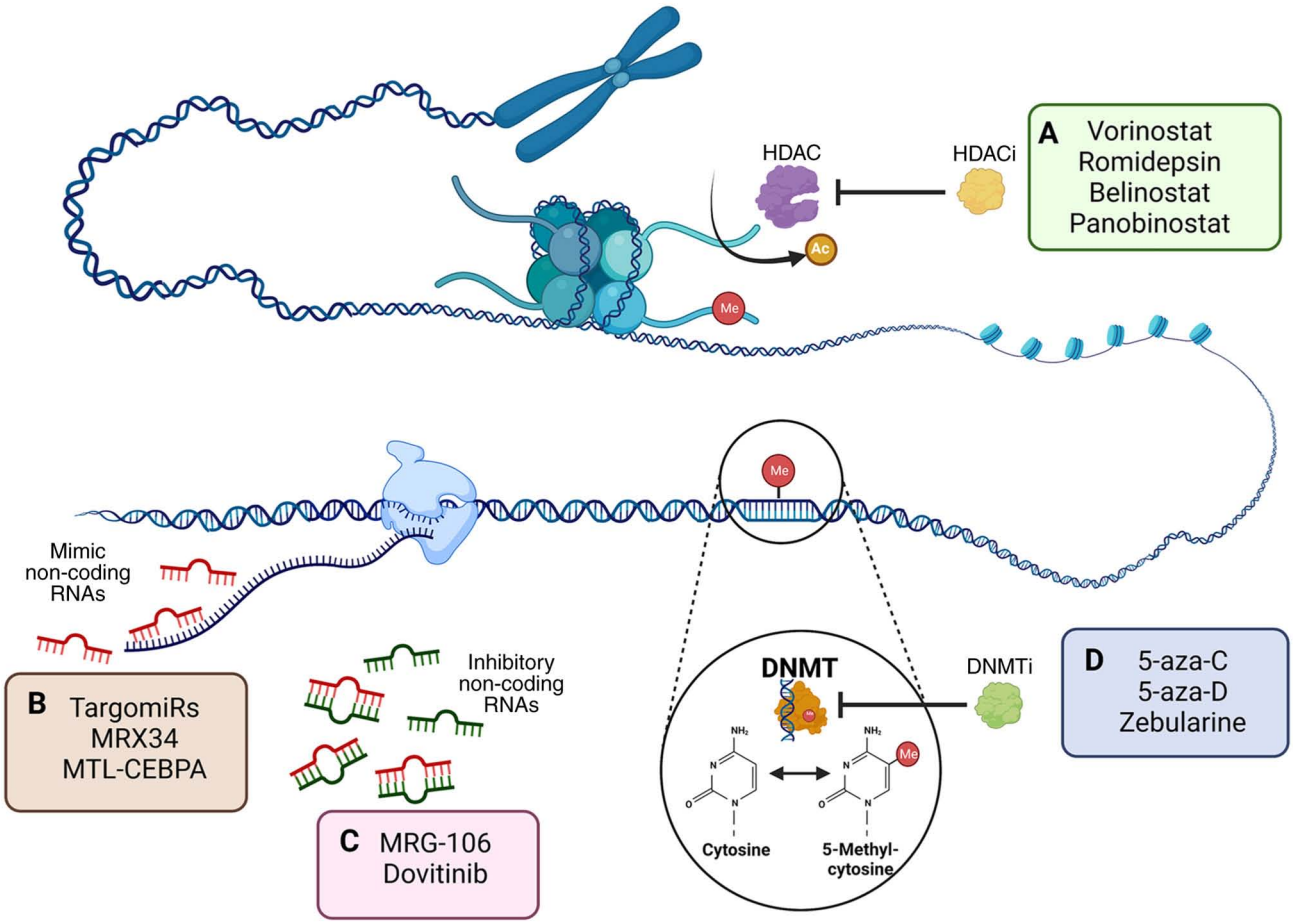

Figure 3. Inhibitor epigenetic modifications and action in cancer. (A) DNA methylation is catalyzed by DNMTs and involves the addition of a methyl group to cytosine, producing 5-methylcytosine. DNMTi, such as 5-aza-C and 5-aza-D, prevent DNA methylation and restore the function of aberrantly silenced genes in cancer. Therapeutic approaches targeting non-coding RNAs in cancer may be directed to one of two aims: (B) Restoring tumor suppressor activity through mimicking molecules (TargomiRs and MRX34) and synthetic RNAs (MTL-CEBPA) or (C) inhibiting oncogene expression through the employment of molecules that promote the degradation of target mRNAs (MRG-106 and Dovitinib). (D) Histone tails in the nucleosome can be post-translationally modified by the covalent attachment of acetyl groups. Histone deacetylation catalyzed by HDAC modifies the histone code. Various HDACi have been approved by the US Food and Drug Administration for their use as antineoplastic drugs, including vorinostat, romidepsin, belinostat and panobinostat. 5-aza-C, 5-azacytidine; 5-aza-D, 5-aza-2'-deoxycytidine; Ac, acetyl group; DNMT, DNA methyltransferase; DNMTi, DNMT inhibitors; HDAC, histone deacetylase; HDACi, HDAC inhibitors; Me, methyl group; MTL-CEBPA, RNA duplex acting of c/ebpa gen transcription; CEBPA, CCAAT/enhancer-binding protein alpha; MRX34, mimic of miR-34a.

and impaired DNA polymerase function (70). Indirect effects on gene expression are mainly mediated by histone modifications, such as acetylation and methylation (71-73). Treatment with 5-aza-D abolished transcription factor RUNX3 silencing through decreased H3K9 methylation, which favored gene expression, independent of changes in promoter methylation (74). Similar effects of 5-aza-D at the p14/p16 locus have been reported in bladder and gastric cancer cells (73,75).

5-aza-D and 5-aza-C are used to treat various hematological cancer types, including AML and MDS, because of their ability to reactivate silenced tumor suppressor genes and DNA damage-induced cell cycle arrest and apoptosis (76). Both drugs induce complete responses and hematologic improvement; however, prolonged overall survival has only been shown for 5-aza-C. Although the drugs only slightly differ in their molecular structures, there are essential differences in their mechanisms of action (Table I) (77). There are >135 epigenetics-related clinical completed studies in different phases (49 in phase 1; 67 in phase 2; 22 in phase 3; and 1 in phase 4); Of which, 17 phase 3 interventional clinical trials using 5-aza-D and 5-aza-C in combination with chemotherapy drugs or immunotherapy in cancer have completed the recruitment stage (Table II) (78).

Zebularine. In the early 1990s, second-generation nucleoside analogs were synthesized, such as zebularine [1-(β-D-ribofuranosyl)-2(1H)-pyrimidinone], a cytidine analog that lacks the amino (N) group at position four of the pyrimidine ring (79). It has high stability under physiological conditions and inhibits DNA methylation through its action on DNMTs and cytidine deaminase, an enzyme responsible for resistance to nucleoside DNA methylation analogs (80). In addition, zebularine has low cytotoxicity, which could translate into longer treatments with low doses to maintain a demethylated state at an acidic or a neutral pH (80). By comparison, 5-aza-C and 5-aza-D exhibit significant toxicity, low instability under physiological conditions and short half-lives (59), which may complicate their use in clinical settings.

Non-nucleoside small-molecule compounds. Furthermore, a chemically diverse group of non-nucleoside small-molecule compounds, such as hydralazine and procainamide have been

Table I. Different effects of 5-aza-C and 5-aza-D in cancer cells.

First author/s, year	Feature	5-aza-C	5-aza-D	(Refs.)
Stresemann and Lyko, 2008	RNA incorporation	80-90%	No	(45)
Stresemann and Lyko, 2008	DNA incorporation	20-40%	100%	(45)
Stresemann and Lyko, 2008	DNA strand breaks	Weaker DNA damage compared with 5-aza-D	Increased DNA damage compared with 5-aza-C	(45)
Stresemann and Lyko, 2008	Demethylating capacity	Weaker DNA demethylating activity than 5-aza-D	90% more than 5-aza-C	(45)
Nguyen *et al*, 2010	Cell cycle	Arrest at phase G_1	Increases the number of cells arrested in G_2 phase and mitosis	(77)
Hollenbach *et al*, 2010	Gene expression	Decreasing the expression of genes related to the cell cycle and metabolic processes	Regulates genes related to cell differentiation	(62)
Zheng *et al*, 2012; Soengas *et al*, 2001	Mechanism of action	Transcriptional regulation and induced hypomethylation	Induced demethylation, removal of methylation, histone modifications or a combination of both	(52,222)

5-aza-C, 5-azacytidine; 5-aza-D, 5-aza-2'-deoxycytidine; n/a, not applicable.

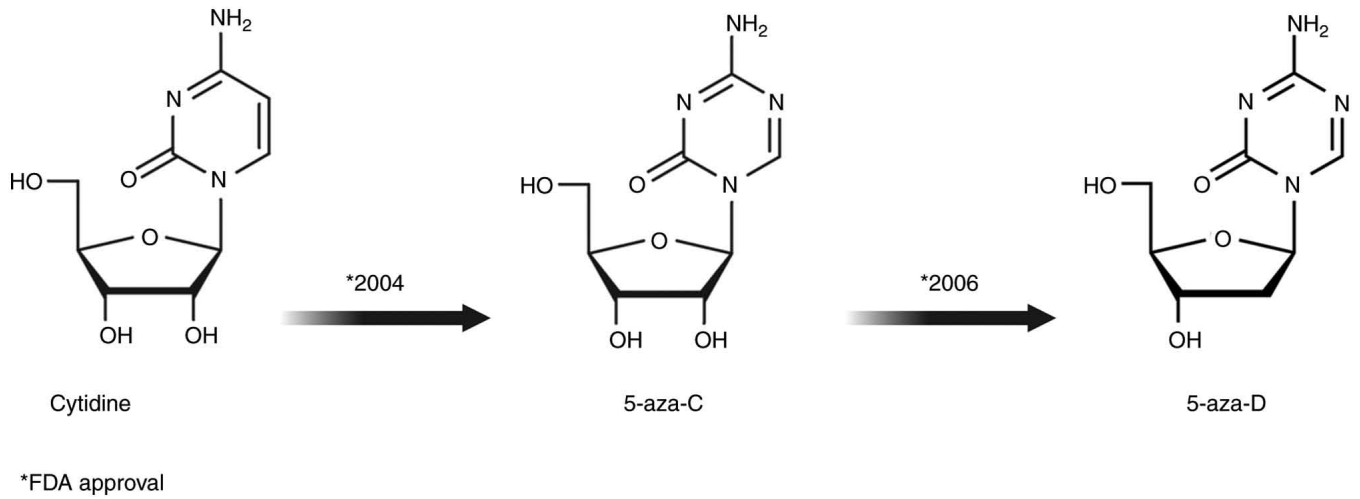

Figure 4. Chemical structures of DNA demethylating agents (cytidine analogs 5-aza-C and 5-aza-D) approved by the United States Food and Drug Administration as antineoplastic drugs. 5-aza-C, 5-azacytidine; 5-aza-D, 5-aza-2'-deoxycytidine.

reported as DNMTi (81-83). These drugs that are not incorporated into DNA or RNA but inhibit DNMT activity alone or in combination with chemo/radiotherapy, have shown promising results in various cancer types (82). Other small-molecule compounds, such as guadecitabine, epigallocatechin-3-gallate (EGCG), RG-108 and MG98, exhibit a DNA hypomethylating effect either through the competitive inhibition or through the degradation of DNMT (46,84). In addition, the inhibition of histone acetylation and generation of reactive oxygen species are effects associated with the treatment with biologically active non-nucleoside compounds (85,86).

Covalent histone modifications in cancer. In eukaryotic cells, 145-147 bp DNA is wrapped around histone octamers, comprising a core of histone dimers 2A, H2B, H3 and H4, to form nucleosomes, the basic units of chromatin. Histone tails extending from the core of the nucleosome can be post-translationally modified by methylation, acetylation, phosphorylation, SUMOylation and ubiquitination (Fig. 1) (87). Histone modifications serve essential roles in various cellular processes, including DNA repair, replication, stemness and changes in cell state (88). Aberrant histone post-translation modifications occur during the initiation and progression of cancer (89).

Table II. Interventional clinical trials of DNA demethylating agents 5-aza-C and 5-aza-D in cancer.

Drug	Cancer type	Therapeutic approach	ClinicalTrials.gov identifier
5-aza-C	Patients newly diagnosed with AML	Talirine combined with 5-aza-C or 5-aza-D	NCT02785900
	Adults with AML	Pracinostat in combination with 5-aza-C	NCT03151408
	MDS	Comparing the efficacy and safety of Eltrombopag in combination with 5-aza-C vs. placebo plus 5-aza-C	NCT02158936
	Relapse or refractory DLBL	Avelumab in combination regimens that include an immune agonist, 5-aza-C, a CD20 antagonist and/or conventional chemotherapy	NCT02951156
	AML	Venetoclax in combination with 5-aza-C vs. 5-aza-C alone	NCT02993523
	AML with *flt3* gene mutation	Gilteritinib plus 5-aza-C or 5-aza-C alone	NCT02752035
	AML with *idh2* gene mutation	AG-221 (a small molecule inhibitor of the IDH2 enzyme) compared with BSC only, 5-aza-C plus BSC, low-dose cytarabine plus BSC, or intermediate-dose cytarabine plus BSC	NCT02577406
	AML with *idh1* gene mutation	Ivosidenib vs. placebo in combination with 5-aza-C	NCT03173248
	MDS	MBG453 or placebo added to 5-aza-C	NCT04266301
	AML	5-aza-C with or without nivolumab or midostaurin, or 5-aza-D and cytarabine alone	NCT03092674
	AML	Vadastuximab talirine vs. placebo in combination with 5-aza-C or 5-aza-D	NCT02785900
5-aza-D	Metastatic TNBC	5-aza-D plus carboplatin	NCT03295552
	Ovary cancer	Lower dose 5-aza-D plus carboplatin-paclitaxel regimen	NCT02159820
	MDS with P53 mutation	5-aza-D and arsenic trioxide	NCT03377725
	AML	Standard combination chemotherapy plus 5-aza-D	NCT02172872
	AML	Clofarabine or daunorubicin hydrochloride and cytarabine followed by 5-aza-D	NCT02085408
	AML	5-aza-D with or without nivolumab or midostaurin, or cytarabine and 5-aza-D alone	NCT03092674

5-aza-C, 5-azacytidine; 5-aza-D, 5-aza-2'-deoxycytidine; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; TNBC, triple-negative breast cancer; DLBL, diffuse large B-cell lymphoma; *flt3*, fms related receptor tyrosine kinase 3; IDH2, isocitrate dehydrogenase; BSC, best supportive care; MBG453, sabatolimab.

Histone acetylation and deacetylation. Two families of antagonistic enzymes control histone acetylation: Histone acetyltransferases (HATs), which acetylate lysine residues at the N-terminus of histone proteins, and HDACs, which remove acetyl groups from histones. Histone acetylation reduces attraction between negative and positive charges of DNA and histone tails, respectively (90,91). This structural change favors the decompaction of chromatin, allowing access to the gene sequence for its transcription. The altered activity of HATs observed in several types of cancer, including esophageal, lung and liver cancer, has been associated with the aberrant activation of genes whose expression is necessary for maintaining tumor growth (92-94). Chemical modifications to histones form the basis of histone codes and may be associated with gene expression or silencing (88). Based on their sequence similarities to yeast HDACs, the 18 identified human HDACs are divided

Table III. Effects of HDACs on carcinogenesis.

HDAC	Cancer types	Substrate (histone and non-histone)	Cellular processes affected
HDAC1	Lung, gastric, liver, breast, ovarian, prostate, renal, bladder and hematological	H4K16 and H3K56	Differentiation, proliferation, metastasis, apoptosis and cell cycle
HDAC2	Medulloblastoma, gastric, pancreatic, colorectal, breast, ovarian, prostate, renal, bladder and hematological	H4K16 and H3K56	Differentiation, proliferation, metastasis, apoptosis and cell cycle
HDAC3	Lung, gastric, breast, ovarian, prostate, bladder, melanoma and hematological	H3K9, H3K14, H4K5 and H4K12	Differentiation, proliferation, metastasis, apoptosis, cell cycle and inflammation
HDAC4	Hematological (lymphoblastic leukemia) and colorectal tumors	Not defined	Angiogenesis
HDAC5	Hematological, bladder, renal, breast, medulloblastoma	p53	Proliferation, angiogenesis apoptosis and cell cycle
HDAC6	Hematological (lymphoblastic leukemia)	α-tubulin, HSP90 and cortactin	Inflammation, metastasis, angiogenesis, cell cycle and apoptosis
HDAC7	Hematological (lymphoblastic leukemia)	Not defined	Angiogenesis and proliferation
HDAC8	Neuroblastoma, melanoma and hematological	ERRα	Differentiation, apoptosis and cell cycle
HDAC9	Hematological	Not defined	Proliferation and apoptosis
HDAC10	Cervical tumors and chronic lymphocytic leukemia	Not defined	Angiogenesis and cell cycle
HDAC11	Lung, mixed lobular and ductal breast carcinoma, mantle cell lymphoma and myeloproliferative neoplasms	Not defined	Proliferation and survival
SIRT1, SIRT2, SIRT3, SIRT6 and SIRT7	Breast, head and neck, non-small cell lung, colon, prostate, ovarian, gastric, melanoma and hepatocellular	H4K16, H3K9, H3K18, H3K56, H4K16, p53, p73, PTEN, FOXO1, FOXO3a, FOXO4, NICD, MEF2, HIF-1α, HIF-2α, TAF(I)68, SREBP-1c, β-catenin, RelA/p65, PCAF, TIP60, p300, SUV39H1, H4K16, H3K56, α-tubulin and ATP-citrate lyase SETD8	Differentiation, proliferation, metastasis, apoptosis, cell cycle and inflammation

H3K/H4K, histone 2/4 lysine; HIF, hypoxia-inducible factor; HDAC, histone deacetylase; MEF2, myocyte-specific enhancer factor 2; NICD, Notch 1 intracellular domain; PCAF, P300/CBP-associated factor; SIRT, sirtuin; SUV39H1, suppressor of variegation 3-9 homolog 1; ERRα, estrogen-related receptor α; FOXO, forkhead box transcription factors; TAF(I)68, TBP-associated factor; SREBP-1c, sterol regulatory element-binding protein-1c; SETD8, SET domain-containing protein 8.

into four classes: i) Class I isoenzyme HDACs, which include HDAC1, HDAC2, HDAC3 and HDAC8; ii) class II HDACs, which are homologous to yeast protein lysine deacetylase and are further divided into class IIa (including HDAC4, HDAC5, HDAC7 and HDAC9) and class IIb (HDAC6 and HDAC10) subgroups; iii) class III HDACs are similar to yeast sirtuins (SIRTs), and include SIRT1-SIRT7; and iv) class IV HDACs, which comprise only HDAC11 (95). SIRTs are NAD^+-dependent enzymes, whereas the other three classes are zinc cation (Zn^{2+})-dependent HDACs (96).

Table IV. HDACi approved by the US FDA for cancer treatment and their effects on cellular processes.

First author/s, year	HDACi	Target HDAC	Target cellular processes	Type of cancer	Year approved by the FDA	(Refs.)
Bubna, 2015; Mann *et al*, 2007	Vorinostat (SAHA)	Class I and II	Induces cell cycle arrest and apoptosis; inhibits angiogenesis, and downregulates immunosuppressive interleukins	CTCL	2006	(115, 223)
Grant *et al*, 2010	Romidepsin (FK288)	Class I	Induces differentiation, cell cycle arrest and apoptosis	CTCL	2009	(224)
Poole, 2014	Belinostat (PXD101)	Class I, II and IV	Induces apoptosis through the reactivation of suppressor genes	Peripheral T-cell lymphoma	2014	(124)
Moore, 2016	Panobinostat (LBH589)	Pan	Induces cell cycle arrest and apoptosis	CTCL and multiple myeloma	2015	(225)

CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylase; HDACi, HDAC inhibitors; SAHA, suberoylanilide hydroxamic acid; US FDA, United States Food and Drug Administration.

HDACs serve a role in primary biological functions, such as transcription, metastasis (97), autophagy, cell cycle (98), DNA damage repair, angiogenesis (99), stress responses (100) and senescence (101), through histone deacetylation and through non-histone proteins. However, aberrant expression of HDACs can contribute to carcinogenesis by altering gene expression through the deacetylation of different histone residues (Table III) (84). In addition, HDACs can deacetylate non-histone proteins involved in apoptosis, differentiation, cell proliferation control and transcription (102). HDAC upregulation in solid and hematologic tumors promotes tumor suppressor gene silencing or alters gene expression of oncogenic pathways (99). Furthermore, HDAC upregulation is useful for the diagnosis and prognosis of gastric and breast cancer (103).

Histone methyltransferase (HMT). Histone methylation is an essential post-transcriptional modification generally occurring at the lysine and arginine residues of histones H3 and H4 through the addition of methyl groups (104). Mono-, di- or trimethylated states may occur in both lysine and arginine, which subsequently affects transcriptional regulation (88). Histone methylation is mediated by HMTs, of which there are six major classes of histone lysine methyltransferase complexes (KMT1-KMT6) (97,105). The identification of lysine demethylases revealed the reversibility of lysine methylation (106). H3K4-trimethylation (me3), H3K36me3 and H3K79me3 are associated with transcriptional activation, whereas methylation of H3K9me3, H4K20me3 and H3K27me3 is associated with a repressive chromatin state. The interaction and level of methylation of these histone marks serve an important role in transcriptional regulation (103). Furthermore, mutations detected in different cancer types (bladder, melanoma and lung cancer) have been associated with altered activity of methylating enzymes (107). Mutations in enhancer of zeste homolog 2 (EZH2) are found in follicular and diffuse large B-cell lymphomas, gliomas and bone cancers affecting H3K27 (108). The HMT SET domain containing 1A is upregulated in breast cancer, favoring the increase in H3K4me3 in genes associated with migration and metastasis (109). In addition, H3K36me3 is altered in various cancers, such as chondroblastoma, and colon, and head and neck cancer (110,111). These alterations in histone modifications and methylation enzymes contribute to changes in gene expression that may promote carcinogenesis. Therefore, HMT inhibitors have been developed for use as antineoplastic drugs. Clinical trials of protein arginine N-methyltransferase 1, EZH2 and lysine-specific histone demethylase 1 inhibitors have been summarized by Yang *et al* (112).

HDACi for cancer therapy. The increasing understanding of the reversibility of epigenetic processes has led to the identification of drugs that inhibit HDAC activation and prevent tumor development. Four HDACi affecting different cellular processes are FDA-approved (105,113), including vorinostat, romidepsin, belinostat and panobinostat (Fig. 3A; Table IV). Additionally, interventional clinical trials using HDACi in combination with therapeutic drugs for cancer are summarized in Table V.

Vorinostat. Vorinostat (also known as suberoylanilide hydroxamic acid) is a class I- and class II HDACi structurally belonging to the hydroxamate group; it does not inhibit

Table V. Interventional clinical studies of HDACi agents in cancer.

HDACi	Cancer type	Treatment	ClinicalTrials.gov identifier
Vorinostat (SAHA)	Small cell lung	Carboplatin and etoposide in combination with vorinostat	NCT00702962
	Non-small cell lung	Maximum tolerated dose of the combination of vorinostat, cisplatin, pemetrexed and radiation therapy	NCT01059552
	Pancreatic	Maximum tolerated dose of vorinostat plus radiation therapy	NCT00831493
	Breast	Combination of lapatinib and vorinostat	NCT01118975
	Metastatic or recurrent gastric	Vorinostat plus capecitabine and cisplatin	NCT01045538
Romidepsin (FK288)	Non-small cell lung	Romidepsin in combination with erlotinib hydrochloride	NCT01302808
	Pancreatic	Romidepsin (depsipeptide) in combination with gemcitabine	NCT00379639
	HPV^+ nasopharyngeal, HPV^+ cervical and liposarcoma	5-aza-D in combination with romidepsin	NCT01537744
Belinostat (PXD101)	Solid tumors	PXD101 alone and in combination with 5-fluorouracil	NCT00413322
	Ovarian	Belinostat plus carboplatin or paclitaxel or both	NCT00421889
	Non-small cell lung	PXD101 in combination with paclitaxel plus carboplatin in chemotherapy-naïve patients	NCT01310244
	Neuroendocrine	Belinostat in combination with cisplatin and etoposide	NCT00926640
	Small cell lung Malignant epithelial		
Panobinostat (LBH589)	Soft tissue sarcoma	Panobinostat alone	NCT01136499
	Breast	Combination of panobinostat and letrozole	NCT01105312
	Small cell lung	Combination of panobinostat, etoposide and cisplatin	NCT01160731
	Renal	Combination of panobinostat and sorafenib	NCT01005797
	Prostate	Panobinostat in combination with docetaxel and prednisone	NCT00663832
	Pancreatic	Panobinostat in combination with bortezomib	NCT01056601
	Thyroid	Panobinostat alone	NCT01013597
	Brain	Panobinostat alone	NCT00848523
	Hodgkin Lymphoma	Panobinostat alone	NCT00742027
	Non-Hodgkin Lymphoma	Combination of panobinostat and ketoconazole	NCT00503451

HDACi, histone deacetylase inhibitors; HPV, human papillomavirus; SAHA, suberoylanilide hydroxamic acid.

class III HDACs (114). Vorinostat binds to zinc in the catalytic site of HDAC, which blocks the access of target proteins and inhibits its HDAC activity (115). Therefore, this HDACi can modify expression of proteins through structural changes on chromatin, but also by modifying the activity of non-histones proteins (p53, EKLF, E2F1, HIF-1 and GATA) (115,116). Clinical studies have demonstrated that vorinostat treatment reduced solid tumors when administered alone or in

Table VI. Examples of replacement therapies for non-coding RNAs.

First author/s, year	Target	Role in cancer	Therapeutic approach	Effect	(Refs.)
Gilles and Slack, 2018	*let-7* miRNA	Low *let-7* expression is associated with inferior survival in different types of cancer	Synthetic *let-7b* is delivered directly by adenovirus and lentivirus	Reduces NSCLC xenograft tumor growth by targeting *HGMA2*, which is commonly upregulated in NSCLC	(226)
Segal *et al*, 2020			Synthetic *let-7b* miRNA conjugated with lipophilic moieties		(227)
Wu *et al*, 2015; Pan *et al*, 2021; Li *et al*, 2021			*let-7* agomirs, which are chemically modified and end-labeled miRNAs that mimic endogenous miRNAs but with increased stability	Its use decreases invasion and migration of cholangiocarcinoma, sensitizes epithelial ovarian cancer to cisplatin treatment, and inhibits hepatocellular carcinoma	(228-230)
Hong *et al*, 2020	miR-34a	Commonly lost or downmodulated in various solid tumors	MRX34 is a liposomal formulation for restoring miR-34a	Reduction of Bcl-2, DNAJB1, CTNNB1, FOXP1 and HDAC1 expression levels	(231)
van Zandwijk *et al*, 2017; Winata *et al*, 2017	miR-15/16	Downregulated in chronic lymphocytic leukemia, melanoma, colorectal and bladder cancer, and other solid tumors	TargomiRs comprising miRNA mimics based on the miR-15/16 consensus sequence, packaged in EDVs (non-living bacterial minicells) that allow for efficient packaging of nucleic acids and targeting moiety. The EDVs are targeted to anti-EGFR-specific antibodies	In various cancer types, increased levels of the miR-15/16 family result in tumoral growth inhibition	(232,233)
Filippova *et al*, 2021; Williams and Pickard, 2016; Liu *et al*, 2021	*GAS5* lncRNA	Tumor suppressor in multiple solid tumors	This is a stem-loop structure within the GAS5 hormone response element mimic	Cell lines exhibit increased apoptosis and reduced cell proliferation	(234-236)

Table VI. Continued.

First author/s, year	Target	Role in cancer	Therapeutic approach	Effect	(Refs.)
Smaldone and Davies, 2010	*H19* lncRNA	Highly expressed in malignant tissue but low or undetectable in adult tissue	BC-819 is a double-stranded DNA plasmid that codes for diphtheria toxin A driven by the *H19* promoter and is selectively expressed in tumor cells	Selective toxin expression results in selective tumor cell destruction through the inhibition of protein synthesis in the tumor cells	(237)
Zhao *et al*, 2019; Reebye *et al*, 2014	CEBPA-saRNA	A transcriptional regulator that serves a key role in maintaining liver function; its expression is lost in HCC	MTL-CEBPA comprises a double-stranded RNA formulated into a SMARTICLES® liposomal nanoparticle	CEBPA-saRNA reduces tumor burden and simultaneously improves liver function in HCC	(238,239)

HCC, hepatocellular carcinoma; HDAC, histone deacetylase; lncRNA, long non-coding RNA; miR/miRNA, microRNA; NSCLC, non-small cell lung cancer; saRNA, small activating RNA; DNAJB1, DnaJ heat shock protein family (Hsp40) member B1; HMGA2, high mobility group AT-hook 2; CTNNB1, catenin β1 gene; FOXP1, forkhead box protein P1; TargomiRs, miRNA mimics based on the miR-15/16 consensus sequence; EDVs, extracellular directed vesicles; MTL-CEBPA, RNA duplex activating of the *c/ebpa* gen transcription; CEBPA, CCAAT/enhancer-binding protein alpha; CEBPA-saRNA, CCAAT/enhancer-binding protein α-small activating RNA.

combination with alkylating agents, proteasome inhibitors, anthracyclines and antiangiogenic and/or antimetabolite agents (78,113,117,118).

Romidepsin (Istodax®). Romidepsin is a bicyclic peptide derived from *Chromobacterium violaceum* and is a class I HDACi (particularly against HDAC1, HDAC2, HDAC3 and HDAC8) with only weak activity against class II HDACs (119). Its mechanism of action is based on binding to zinc in the pocket domain of HDACs, inhibiting the interaction with target proteins (120). Treatment with romidepsin shows promising effects in hematological tumors, such as cutaneous T-cell lymphoma and other peripheral T-cell lymphomas (PTCLs), with clinical studies demonstrating a reduction in solid tumors, including colon, sarcoma, breast and renal cancer (121). Furthermore, romidepsin has been used in combination with other cancer treatments, including cisplatin, paclitaxel, CC-486 and 5-aza-D, which are safe and effective for solid and hematological tumors (122).

Belinostat. Belinostat has been used as a monotherapy to treat relapsed or refractory PTCL (123). Belinostat is a hydroxamate-type inhibitor of class I, II and IV HDACs; however, its mechanism of action has not yet been elucidated (124). Nevertheless, clinical studies have used belinostat to treat solid tumors, including colon, breast, pancreas, prostate and bladder cancer (78). Furthermore, belinostat has been reported to act synergistically with the proteasome inhibitor bortezomib and with the alkylating agents cisplatin and carboplatin against solid tumors *in vitro* (78,125,126).

Panobinostat. Panobinostat is a pan-HDACi belonging to the hydroxamate family. Some clinical studies have tested its use alone or in combination with other drugs to particularly treat solid tumors, such as sarcoma, breast, lung, renal, prostate, pancreas, thyroid and malignant brain cancer, including hematological cancer types such as Hodgkin and non-Hodgkin lymphoma; however, the mechanism of action is uncharacterized (78,127).

3. ncRNAs in epigenetic control

In addition to DNA methylation and histone modifications, ncRNAs also serve a key role in epigenetic control (Fig. 1). ncRNAs are divided into two main groups: Housekeeping and regulatory ncRNA. Housekeeping ncRNAs include transfer RNAs, ribosomal RNAs, small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs), which enable the flow of genetic information from DNA to proteins (128,129). snRNAs and snoRNAs participate in the modulation of alternative splicing, which drives mRNA maturation (130). In some instances, these splicing-devoted ncRNAs have epigenetic regulatory functions, as is the case with snRNAs U1 and 7SK, which modulate transcription (130). U1 is associated with the general transcription initiation factor transcription factor IIH (131), and 7SK interacts with the chromatin factor and transcriptional regulator high mobility group AT-hook 1 (132).

By contrast, regulatory ncRNAs are non-constitutively expressed RNAs that serve roles in epigenetic control by modulating chromatin structure, RNA polymerase activity and mRNA stability. Regulatory ncRNAs are divided

Table VII. Interventional clinical trials of replacement therapies for non-coding RNAs.

Therapeutic oligonucleotide	Cancer type	Therapeutic approach	ClinicalTrials.gov identifier
MRX34	Primary liver cancer or other selected solid tumors and hematologic malignancies	Monotherapy with MRX34 to investigate the safety and tolerability of escalating doses	NCT01829971
TargomiRs	Recurrent malignant pleural mesothelioma and non-small cell lung cancer	Single-drug TargomiR	NCT02369198
DTA-H19	Unresectable, locally advanced pancreatic cancer and advanced-stage ovarian cancer	Monotherapy intratumoral with DTA-H19	NCT00826150
	Non-muscle invasive bladder cancer	Monotherapy BC-819 instilled intravesical into the bladder	NCT03719300
	Superficial transitional cell bladder carcinoma and locally advanced pancreatic adenocarcinoma	BC-819 and bacillus Calmette-Guérin vaccine	NCT01878188
BC-819 (inodiftagene vixteplasmid)	Advanced HCC	BC-819 and gemcitabine	NCT01413087
	Lung, ovarian, pancreatic, gall bladder, HCC, neuroendocrine, and cholangiocarcinoma	Monotherapy or in combination with sorafenib	NCT02716012
MTL-CEBPA	Solid tumor in adult population	MTL-CEBPA in combination with a PD-1 inhibitor pembrolizumab	NCT04105335
	Advanced HCC	MTL-CEBPA plus sorafenib or sorafenib alone	NCT04710641
	Advanced HCC	MTL-CEBPA, atezolizumab and bevacizumab	NCT05097911

HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; TargomiR, miRNA mimics based on the miR-15/16 consensus sequence; MTL-CEBPA, RNA duplex activating of the c/ebpa gen transcription; CEBPA, CCAAT/enhancer-binding protein α; MRX34, mimic of miR-34a; DTA, DNA plasmid that carries the gene for the diphtheria toxin A.

according to length: Small [small non-coding RNA (sncRNA); ≤200 nucleotides] and long [long non-coding RNA (lncRNA); >200 nucleotides] (128). The best-understood sncRNAs are miRNAs/miRs and small interfering RNAs (siRNAs). Other small ncRNAs include trans-acting siRNAs, small-scan siRNAs, repeated-associated siRNAs and piwi-interacting RNAs (piRNAs) (133,134). Classification of lncRNAs is even more complex, and efforts have been made to obtain more comprehensive annotations. Thus, one classification system for lncRNAs involves four subdivisions: i) Long intergenic non-coding RNAs (lincRNAs) and intronic lncRNAs; ii) sense and antisense lncRNAs; iii) cis- or trans-acting lncRNAs; and iv) transcriptional or post-transcriptional lncRNAs (135). Notably, the function of several lncRNAs remains unknown; therefore, they are denoted as non-functional RNAs and considered as transcriptional noise (136). Circular RNAs (circRNAs) can be consider as lncRNAs in terms of size (mean length ~50 nt); however, due to their structure, some authors consider them as a third group of ncRNAs (137). They comprise between one and five exons and flanking introns, but differ from the previously mentioned lncRNAs since they are single-stranded RNA that form a loop by covalently joining their 5' and 3' ends (135).

sncRNAs in cancer. siRNAs and miRNAs are the most understood sncRNAs. They are double-stranded RNAs (dsRNAs) whose genesis and function partially overlap. Both can promote RNA interference (RNAi), a post-translational regulatory mechanism that provokes gene silencing through mRNA degradation (138). The genesis of siRNAs and miRNAs relies on Dicer, an RNase III enzyme that cleaves dsRNAs (139). A capped and polyadenylated RNA with a stem-loop structure is cleaved by Drosha to form genetically coded precursor miRNAs (pre-miRNAs) (140). miRNA genes are transcribed in the cell nucleus by RNA polymerase II giving rise to primary miRNAs (pri-miRNA) (141). Pre-miRNAs and dsRNAs are

Table VIII. Inhibitory non-coding RNAs in cancer therapy.

First author/s, year	Type	Target	Role of target in cancer	Mechanism of action	Effects	(Refs.)
Seto *et al*, 2018	ASO	miR-155	miR-155 is associated with poor prognosis in lymphoma and leukemia	Cobomarsen (MRG-106) is a locked nucleic acid-modified ASO inhibitor of miR-155	Inhibition of miR-155 reverses malignant tumor phenotype by inducing apoptosis	(240)
Ijaz *et al*, 2018; Ohanian *et al*, 2018	ASO	*Grb2*	*Grb2* is involved in the progression and development of different cancer types	L-*Grb2* ASO (BP1001) comprises an antisense oligodeoxynucleotide targeted against the translation initiation site of the *Grb2* transcript	*Grb2* gene inhibition results in reduced proliferation of cancer cells and enhanced survival of mice bearing leukemia xenografts	(241,242)
Golan *et al*, 2015; Timar and Kashofer, 2020	siRNA	*KRAS* mRNA	KRAS is mutated in ~30% of all tumor cases	System LODER® (Local Drug EluteR), a miniature biodegradable polymeric matrix for local drug release of KRAS (G12D) siRNA within the tumor	*KRAS* inhibition induces inhibition of tumor growth and induction of apoptosis in tumor cells In mice, survival rates are improved	(243,244)
Zhang *et al*, 2021; Shortridge *et al*, 2022	Small molecule inhibitor	miR-21	miR-21 is an antiapoptotic factor in cancer cells and is upregulated in breast, ovarian and lung cancer, as well as in glioblastomas	ITX-0052 is a small molecule that exhibits strong binding activity to pre-miR-21, inhibiting its processing Dovitinib (TKI258) is a tyrosine kinase small-molecule inhibitor that selectively targets the precursor of-miR-21	These compounds reduce cellular proliferation and miR-21 expression levels in cancer cell lines and increase various tumor suppressor protein expression levels	(245,246)
Donlic *et al*, 2018; Goyal *et al*, 2021		MALAT1 lncRNA	MALAT1 is upregulated in multiple cancer types	Diphenylfuran analogs targeted at the triple helix structure of MALAT1 lncRNA	In non-small cell lung cancer, knockdown of MALAT1 inhibits tumor growth and metastasis by downregulating PI3K/AKT signaling	(247,248)

ASO, antisense oligonucleotide; FGFR, fibroblast growth factor receptor; lncRNA, long non-coding RNA; miR, microRNA; siRNA, small interfering RNA; Grb2, growth factor receptor-bound protein 2; L-Grb2, liposomal antisense oligodeoxynucleotide directed to Grb2; MALAT1, metastasis associated lung adenocarcinoma transcript 1.

Table IX. Interventional clinical trials of inhibitory non-coding RNAs.

Therapeutic oligonucleotide	Cancer type	Treatment	ClinicalTrials.gov identifier
Cobomarsen (MRG-106)	CTCL	MRG-106 monotherapy	NCT03837457
	CTCL	MRG-106 or vorinostat	NCT03713320
	CTCL, CLL, ATLL, and DLBCL	MRG-106 monotherapy	NCT02580552
	RAML and ALL	Combination of BP1001 and concurrent low-dose Ara-C	NCT01159028
Dovitinib (TK1258)	mRCC	Dovitinib vs. sorafenib	NCT01223027
	Solid tumors	Dovitinib monotherapy	NCT02116803

ALL, acute lymphoblastic leukemia; Ara-C, cytarabine; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; BP1001, L-Grb-2 antisense oligonucleotide; RAML, recurrent acute myeloid leukemia; mRCC, metastatic renal cell carcinoma; DLBC, diffuse large B-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma.

processed by Dicer in the cytoplasm and interact with the RNA-induced silencing complex (RISC) (142). The siRNA or miRNA sequence guides RISC to the target mRNA (139). After binding to its target by base pairing, argonaute 2 endonuclease (a part of RISC) cleaves the mRNA, causing gene silencing (138,143).

There are essential differences between siRNAs and miRNAs: siRNAs are molecules 21-23 nucleotides long that can modulate more than one mRNA because they are partially complementary to their targets; whereas miRNAs are 19-25 nucleotides long and highly specific to one mRNA sequence, but they can potentially regulate more than one target gene (138). The partial complementarity of siRNAs with the gene sequence suggests that inhibitory activity is not solely due to the direct degradation of target mRNA by the RISC complex but can also increase the mRNA decay through the rapid deadenylation of target transcripts (144,145). In addition, siRNAs can recruit chromatin-targeted RNAi silencing components to heterochromatin (146).

piRNAs are likely miRNAs that are genetically coded in the piRNA cluster of genes and are highly expressed in gonadal tissue to regulate transposable elements in the germline (147). Precursor piRNAs (pre-piRNAs) are transcribed by RNA polymerase II. Once the newly transcribed RNA leaves the nucleus, pre-piRNAs interact with the germline-specific subclade or argonaute proteins known as PIWI proteins (148). Transgenerational inheritance of piRNAs, such as maternal inheritance through oocytes, alters the progeny phenotype, suggesting that it may contribute to diverse cellular processes over generations (149).

There is strong evidence showing the association between miRNAs and cancer development (150-153). miRNA expression is commonly dysregulated in various tumors and deletion of miRNA genes is also observed in other oncogenic genes (Fig. 2C). For example, miR-15a and miR-16-1 are commonly deleted in B-cell chronic lymphocytic leukemia (154). These miRNAs are tumor suppressors that inhibit the expression of the antiapoptotic factor Bcl-1 (155).

By contrast, miRNAs with oncogenic potential are known oncogenes. The best-studied oncomiR is the miR-17-92 cluster (known as oncomiR-1); it is part of chromosome 13 and includes miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a-1, which are often dysregulated in hematopoietic and solid cancers (156). Transcriptional regulation of miRNAs is also common in cancer. For instance, transcription factors and the tumor suppressor protein p53 are the most commonly mutated genes in several human cancer types (e.g., prostate, ovary, skin, lung and breast cancer), and thus, a high number of dysregulated miRNAs are associated with carcinogenesis (157,158). Notably, the highly mutagenic landscape seen in the p53 gene gives rise to different variants, each with a particular behavior, with specific miRNA targets (159). Notably, several oncoviruses express proteins that inactivate *p53* and consequently alter host miRNAs (160,161).

Therapeutic oligonucleotides are an emerging alternative treatment. The therapeutic potential of miRNAs is delayed through problems associated with the toxicity of the administration methods and biological factors (clearance, non-specific distribution and degradation in circulation) that may affect the efficacy of the molecules. In addition to side effects unwanted related mainly with the possible activation immune response and off-target silencing of RNAs that play essential roles in cell mechanisms. Synthetic RNA molecules improve biostability and reduce toxicity through chemical modifications, such as 20-fluoro-35 and 20-O-methyl, indicating that they may solve some of the problems associated with miRNAs (161).

lncRNAs in cancer. lncRNAs are the most abundant RNA, with 16,000-100,000 known human lncRNA genes (162). They share similarities with mRNAs because they exhibit transcriptional regulation, and a considerable number of them are 3' polyadenylated and 5' capped and undergo lncRNA splicing (159).

lncRNAs modulate gene transcription and epigenetics in the cell nucleus and regulate mRNA stability, protein translation and competing endogenous RNA (ceRNA) in the cytoplasm (163). These RNAs have various mechanisms, such as transmitting transcriptional signals, functioning

as decoys, scaffolds, RNA enhancers or coding for short peptides (163,164).

Signal lncRNAs regulate transcription in response to several stimuli such as inflammatory response, metabolic changes and oxidative stress (163). Their transcription occurs at specific times and locations, thus serving as molecular signals. For example, X-chromosome inactivation occurs during female development (165). The lncRNA *Xist* is transcribed from the X chromosome that will be inactivated, and the sole expression of *Xist* indicates active silencing at the genomic locus. Signal lncRNAs can be classified as decoys or scaffolds (166), and a single lncRNA can have more than one mode of action. For instance, lincRNA-*p21* has essential functions in cancer development by modulating the transcription of *p21* downstream of *p53* activity (167). lincRNA-*p21* expression is a marker of DNA damage and apoptosis (168). However, it is also a scaffold molecule for the transcriptional complex assembled over the *p21* promoter by recruiting heterogeneous nuclear ribonucleoprotein (hnRNP)-K, which mediates *p53* binding to such promoters (169). Furthermore, lincRNA-*p21* interacts with MDM2 proto-oncogene (*MDM2*) to release *p53* from repression (166).

Decoy lncRNAs trap transcriptional regulatory factors by presenting decoy binding sites, thus lowering the availability of elements needed for mRNA transcription (170). Scaffold lncRNAs allow the formation of multiple complexes that either enhance or repress transcription (164). For instance, paraspeckles are mammalian-specific protein-rich nuclear organelles assembled on top of the lncRNA NEAT1. These organelles can trap RNAs and nucleoplasmic proteins, thereby reducing their availability (171). Gastric cancer lncRNA serves as a modular scaffold for the histone-modified components WD repeat-containing protein 5 and lysine acetyltransferase 2A in gastric cancer. It guides these components to target genes to specify histone modification patterns (172). The guiding function of lncRNAs helps direct ribonucleoproteins to target genes, and enhancer lncRNAs influence the three-dimensional organization of DNA (164).

It has been demonstrated that some ncRNAs possess open reading frames encoding peptides (173). pri-miRNAs may encode proteins if transported to the cytosol without processing (174). circRNAs can also be translated into protein through the internal ribosome entry site (IRES) (175). Several lncRNAs have been identified in a number cancer types. For instance, lncRNA *HOXB-AS3* encodes a conserved 53-amino-acid-long peptide that interacts with hnRNPA1 to repress glucose metabolism reprogramming, thus suppressing colon cancer growth (176). Notably, the lncRNA peptidome has been established for colorectal adenocarcinoma (177). Five universally expressed lncRNA peptides show greater expression in tumors than normal tissues, suggesting that they are promising biomarkers for this type of cancer (154). Furthermore, the peptide products of these lncRNAs are more stable than RNA molecules in circulation; therefore, patient plasma can be a reliable sample for diagnosis (178).

circRNAs in cancer. circRNAs are ncRNAs that are similar in length to lncRNAs but they lack 5' and 3' modifications and are covalently linked, forming a closed circular structure (129). These circular structures are usually formed between the 5' and 3' spliced sites of exons, although intron circularization also exists (179). Intronic circRNAs (ciRNAs) are distinguished from exonic circRNAs (180). Exonic circRNAs are transported to the cytoplasm by ATP-dependent RNA helicases, whereas ciRNAs remain in the nucleus and modulate transcription (129).

Cytoplasmic circRNAs act as miRNA sponges that regulate downstream targets or bind proteins (181). For instance, numerous circRNAs are sponges of miR-7, a crucial tumor suppressor in several cancer types. ciRS-7 expression is upregulated in colorectal and gastric cancer, and blocks the suppressive function of miR-7 (181). ciRS-7 contains ~70 conserved miR-7 target sites, and downregulation of this miRNA promotes retinoblastoma and astrocytoma development (182). circZFR binds to different miRNAs and exerts opposing functions; it inhibits gastric cancer proliferation through PTEN upregulation by targeting the miR-130a/107 (183). Conversely, circFZR promotes hepatocellular carcinoma proliferation by modulating miR-1261/4302/3619 (184).

In addition, circRNAs interact with RNA-binding proteins, which regulate RNA transcription, splicing, stability, localization and translation (185). The interaction of circRNAs with proteins acts as either a decoy or a scaffold (186). For instance, circ-DNMT1, originating from the splicing of DNMT1, is upregulated in breast cancer and contributes to cell proliferation (187). It interacts with *p53* and ribonucleoprotein hnRNPD and mediates the nuclear translocation of both proteins (187). The binding of circ-DNMT1 to *hnRNPD* stabilizes DNMT1 mRNA and increases its translation (188). circ-forkhead box O3 (FOXO3) expression serves a determining role in the control of cell cycle progression. The formation of a ternary complex with CDK2 and p21 proteins inhibits the G_1/S transition, mainly by blocking the interaction of CDK2 with cyclin E (189). circ-FOXO3 expression is dysregulated in tumor cells (breast and renal cancer), while, under oxidative stress conditions, its upregulation is associated with cell cycle arrest and apoptosis (190). The interaction of Circ-FOXO3 with MDM2 facilitates p53 ubiquitination in the cytosol, which reduces FOXO3 degradation by MDM2 and upregulates the expression of the *p53* upregulated modulator of apoptosis gene (187).

Some circRNAs can be translated into peptides due to IRESs or N6-methyladenosine modifications (184). For example, circ-FBXW7 encodes a 21 kDa protein that inhibits cancer cell proliferation and reduces c-Myc half-life; its expression is positively associated with the overall survival of patients with glioblastoma (191).

ncRNAs as therapeutic tools in cancer. RNA-based therapy is an expanding drug category with rapid success found through the development of an mRNA-based vaccine against severe acute respiratory syndrome coronavirus-2 to tackle the coronavirus disease 2019 pandemic (192). ncRNA-based therapies are aimed at modulating the transcriptional or post-transcriptional expression of endogenous mRNAs to control the expression of specific proteins involved in cancer development (193). Most ncRNA therapies are based on miRNAs because they potentially target several genes simultaneously, which is useful in multigenetic diseases (137). However, this multi-target action may also have off-target drawbacks, and thus, siRNAs are preferred for target identification and drug

discovery (138). Similarly, lncRNAs may be used to directly target or modulate other molecules, such as miRNAs, with various molecules reaching the clinical trial phase (194). To the best of our knowledge, there are no current preclinical reports using circRNAs alone as targets or therapeutic vectors for cancer treatment; however, this will likely change in the future (195).

Targeting ncRNAs in cancer serves one of two aims: To restore tumor suppressor activity or to inhibit oncogene expression (Fig. 3C). The ncRNA may directly related with activation of genes controlling growth and differentiation cellular, or promote the transformation through indirect inhibition of genes of downstream pathways (196). In the second case, ncRNAs modulate gene expression through RNAi or through transcriptional gene silencing, which can result in long-term stable, inheritable epigenetic changes (197). This second mechanism is more commonly described for lncRNAs and RNAi than for sncRNAs, although both types of ncRNAs can exert each mode of action (144).

ncRNA replacement therapy (mimics). Replacement therapy involves delivering mimicking molecules, synthetic RNA (particularly sncRNA), to restore downregulated targets (Fig. 3B) (198). Exogenous inhibitory RNAs mimic tiers in the RNAi pathway; synthetic RNAs can be delivered to cells in three ways. The first is artificial miRNAs (amiRNAs), which are equivalent to endogenous pri-miRNAs. amiRNAs are double-stranded stems flanked by a single-stranded basal segment and an apical loop containing a recombinant pri-miRNA scaffold and siRNA insert (199). These synthetic RNAs enter the cell nucleus, undergo Drosha processing and are exported to the cytoplasm to be loaded into the Dicer complex. Therapeutically, amiRNAs can exert a long-lasting effect due to their stable expression, which implies treatment regimens with few doses, thus reducing the risk of toxicity. In addition, they do not saturate miRNA machinery (198). Second, vector-based short hairpin RNAs are the most widely used molecules for silencing in mammalian cells. They mimic pre-miRNAs, which are processed double-stranded stem-loop molecules that undergo Dicer processing. Third, synthetic siRNAs are molecules of dsRNA that can be directly processed by Dicer in a similar manner to miRNAs (198,199). This last group includes small activating RNAs (saRNAs), which are dsRNAs that specifically target and activate promoters. saRNAs are processed by argonaute proteins, which translocate as a complex to the nucleus, bind to the promoter to open the chromatin, and recruit positive transcriptional regulators to the complex (200). Tables VI and VII present examples of ncRNAs associated with cancer development and therapeutic approaches applied in clinical trials.

ncRNA inhibition therapy. Inhibition therapy depletes oncogenic ncRNA expression. Antisense oligonucleotides (ASOs) are 18-30 bp in length and bind to target mRNAs and promote their degradation by RNAse H, which recognizes the DNA:RNA hybrid and cleaves the RNA in the complex (201). Alternatively, ASOs can bind to miRNAs [anti-miRNA oligonucleotide (AMOs) also known as antagomirs] (202). ASOs and AMOs are subjected to nuclease degradation and weakly bind to proteins; thus, their stability and uptake must be improved by specific chemical modifications (201). One such modification is locked nucleic acids (LNAs), a methylene linkage connecting the 2' and 4' carbons of the RNA backbone ribose (203). BlockmiRs are another class of ASOs that specifically target the miRNA binding site in mRNAs, thus blocking miRNA binding (204).

Aptamers are a class of synthetic DNA or RNA oligonucleotides that target proteins. They recognize the tertiary or quaternary structure of proteins rather than the linear sequence, as is the case for ASOs; thus, aptamers are also known as chemical antibodies (205). Gapmers are ASOs containing a central DNA flanked by modified oligonucleotides. These molecules are considered powerful options for targeting nuclear lncRNAs due to the high level of RNAse H activity observed during application (206).

Small molecules can also inhibit ncRNAs. These molecules target either RNA-interacting molecules or ncRNAs. For example, bisphenol A and diethylstilbestrol can modify chromatin structure and gene activation via the increased expression of the lncRNA HOTAIR (207). Their advantage over oligonucleotides is that they are easily delivered, soluble, bioavailable, stable and can be designed on a structure-based approach. In addition, some small-molecule inhibitors approved by the FDA can manipulate ncRNAs; this would shorten the time taken to translate experiments to clinical therapy (208).

Endogenously expressed lncRNAs and circRNAs function as ceRNAs by sequestering miRNAs (209). This inherent ability of lncRNAs to block the activity of miRNAs was exploited to engineer decoys, also referred to as target mimics or sponges (177). Both lncRNAs and artificial sponges harbor short sequences that are homologous to miRNA binding sites on their endogenous targets (210). Therefore, decoys sequester miRNAs and prevent their binding to targets (211). Engineered sponges typically contain 10 binding sites separated by a few nucleotides (212). Sponges with imperfect binding sites provoking a bulge are more effective in attracting miRNAs and are more stable (213). Tough decoys are 60-bp-long harpin sponges with an internal bulge containing two miRNA sites (214).

The CRISPR-CRISPR associated protein 9 (CRISPR-Cas9) toolbox enables the manipulation of genes based on RNA-guided DNA recognition (193). A single-guide RNA is used to mediate DNA endonuclease Cas-9 to introduce gaps into the DNA; thus, CRISPR-Cas9 is designed to remove DNA fragments from the genome (215). The addition of donor DNA with the CRISPR-Cas9 system may cause DNA breakage through homology-directed repair, which uses and introduces the donor DNA into the genome. Although several studies have confirmed the potential therapeutic value of CRISPR-Cas9, there are still concerns regarding off-target effects and ethical concerns raised by this technique in germline cells (216-219). Tables VIII and IX present examples of ncRNA-inhibitory therapies and clinical trials for cancer, respectively.

4. Conclusions

Although carcinogenesis has a complex and multifactorial origin, alterations in epigenetic processes are considered among the first genomic aberrations that occur during cancer development and are closely related to its progression. The dynamic and reversible nature of epigenetic modifications

has allowed the use of epidrug agents that improve cancer treatment, including reducing chemoresistance. Although the use of epidrugs in combination with chemotherapeutic agents may have clinical benefits, several issues must be considered. The reversible nature of methylation patterns persists after drug treatment, and re-methylation and silencing are major unresolved issues. The toxicity and instability of 5-aza-C and 5-aza-D may complicate their use in clinical settings under physiological conditions (59,62). Furthermore, the lack of specificity of the methylating agent may result in the activation of normally silenced genes and contribute to tumorigenesis (62); this poses a significant obstacle in epigenetic therapy.

ncRNAs also represent an essential epigenetic mechanism. Thousands of ncRNAs have been identified and their roles in carcinogenesis are defined. This enables their clinical application through the development of ncRNA-based diagnostic kits for the early detection of cancer and for anticancer therapy. However, this field is not as successful as epidrugs because there is still a large gap between the identification of functional ncRNAs and their clinical applications. In addition, delivery-associated toxicity, poor transfection efficiency, systemic clearance, non-specific biodistribution, degradation in circulation and rapid renal clearance, have delayed the therapeutic potential of ncRNAs (220,221).

The use of epidrugs promises to be an effective tool to help overcome drug resistance in some patients with cancer, particularly for hematological cancer types. However, multidisciplinary work is needed to optimize drug engineering and to design clinical trials to assess the safety and scope of these drugs in cancer therapy for solid tumors.

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Authors' contributions

LJCM, EVU, CS, ML, EDLCH and ACP performed the bibliographic review and wrote and critically revised the manuscript. ACP conceived and directed the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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