

Epigenetic actions of environmental factors and promising drugs for cancer therapy (Review)

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Abstract. Carcinogenesis is known to be primarily associated with gene mutations. Recently, increasing evidence has suggested that epigenetic events also serve crucial roles in tumor etiology. Environmental factors, including nutrition, toxicants and ethanol, are involved in carcinogenesis through inducing epigenetic modifications, such as DNA methylation, histone deacetylase and miRNA regulation. Studying epigenetic mechanisms has facilitated the development of early diagnostic strategies and potential therapeutic avenues. Modulation at the epigenetic level, including reversing epigenetic modifications using targeted drugs, has demonstrated promise in cancer therapy. Therefore, identifying novel epigenetic biomarkers and therapeutic targets has potential for the future of cancer therapy. The present review discusses the environmental factors involved in epigenetic modifications and potential drug candidates for cancer therapy.

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1. Introduction

Currently, cancer is a major threat human health worldwide. Carcinogenesis is a multi-step process resulting mainly from the activation of oncogenes and the deactivation of tumor-suppressor genes. Etiologically, emerging evidences have demonstrated that epigenetic mechanisms are equally vital to carcinogenesis (1), including the chemical modifications of DNA and histone proteins, post-transcriptional regulation of microRNAs (miRNA)s and associated signaling pathways (2). Epigenetic modifications have been suggested to be a nearly event in carcinogenesis, and maybe useful as potential targets for early diagnosis, cancer treatment and prognosis evaluation (3). Based on the increasing number of studies, the focus of investigations of carcinogenesis mechanisms have also shifted from the genetic to epigenetic (4). Epidemiologically, epigenetic mechanisms are stressed by foreign substances, including xenobiotics and environmental conditions (5). Identifying an association between environmental factors and tumorigenesis may enable the development of personalized epigenetic medicines. In the present review, the environmental factors involved in epigenetic actions of carcinogenesis and the recent advancements in epigenetic drugs for cancer treatment are summarized.

2. Epigenetic modifications

Epigenetic modifications are defined as heritable alterations of gene expression levels induced by environment-gene interactions, including DNA methylation, DNA hydroxy methylation, histone modifications, non-coding RNA and miRNA (1). The manifestations of epigenetic alterations are various post-translational modifications (PTMs), including acetylation, methylation, phosphorylation and ADP-ribosylation (6). PTMs drive local changes in chromatin structure and allow for selective access of transcriptional machinery to the DNA. They can also induce various types of signals, subsequently

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Abbreviations: PTM, post translational modification; HDAC, histone deacetylase; DNMT, DNA methyltransferase; VPA, valproic acid; NGS, next generation sequencing; HMT, histone methyltransferases; LSD, lysine-specific demethylase

Key words: epigenetic modification, environmental factor, promising drug, cancer therapy

Table I. The pattern of DNMT inhibitors and their applications.

Compound	Group	DNMT specificity	FDA approved application	Other applications in malignant tumors	(Refs.)
Azacytidine	Nucleoside	DNMT 1, DNMT3A, DNMT3B	Myelodysplastic syndrome	Acute myeloid leukemia, lung, esophageal, liver, breast, pancreatic, colon, ovarian, prostate, cervical and gastric cancer	(26)
Decitabine	Nucleoside	DNMT 1, DNMT3A, DNMT3B	Myelodysplastic syndrome	Acute myeloid leukemia, lung, esophageal, liver, breast, pancreatic, colon, ovarian, prostate, cervical, gastric, glioblastoma and head and neck cancer	(27)
5-Fluoro-2 deoxycytidine	Nucleoside	Undetermined	None	Colon cancer	(28)
Zebularine	Nucleoside	DNMT 1, DNMT3A, DNMT3B	None	Cholangiocarcinoma, colon, liver, acute lymphoblastic leukemia, prostate, lung, breast and head and neck cancer	(29)
SGL-110	Nucleoside	DNMT 1	None	Ovarian, acute myeloid leukemia and lung cancer	(30)
Mahanine	Non-nucleoside	Undetermined	None	Lung, glioblastoma, cervical, prostate and colon cancer	(31)
Hydralazine	Non-nucleoside	DNMT 1, DNMT3A, DNMT3B	None	Myelodysplastic syndrome, cutaneous t-cell lymphoma, prostate and cervical cancer	(32)
Procaine	Non-nucleoside	DNMT 1	None	Lung, nasopharyngeal and liver cancer	(33)
Procainamide	Non-nucleoside	DNMT 1	None	Lung and breast cancer	(33)
SGL-1027	Non-nucleoside	DNMT 1, DNMT3A, DNMT3B	None	None	(34)
Curcumin	Non-nucleoside	DNMT 1	None	Colon, pancreatic, oral, prostate, breast, cervical, ovarian, lung and liver cancer	(35)
RG108	Non-nucleoside	DNMT 1	None	Prostate, promyelocytic leukemia and breast cancer	(36)
3,6-dihydroxyflavone	Non-nucleoside	DNMT 1	None	Breast, cervical and prostate cancer	(37)
Epigallocatechin gallate	Non-nucleoside	DNMT 1	None	Lung, liver, colon, pancreatic, ovarian, breast, prostate, oral, chronic myeloid leukemia and head and neck cancer	(38)
Parthenolide	Non-nucleoside	DNMT 1	None	Osteosarcoma, bladder, breast, colon, ovarian and pancreatic cancer	(39)
PRIMA-1	Non-nucleoside	DNMT 1, DNMT3A, DNMT3B	None	Pancreatic, lung, thyroid cancer, Ewing sarcoma, breast and ovarian cancer	(40)
Genistein	Non-nucleoside	DNMT 1, DNMT3A, DNMT3B	None	Breast, colon, prostate, acute myeloid leukemia, cervical, oral and liver cancer	(41)
Parthenolide	Non-nucleoside	DNMT 1, DNMT3A, DNMT3B	None	Intracranial glioma, oral, colon and breast cancer	(42)

DNMT, DNA methyltransferase; FDA, Food and Drug Administration.

Table II. Pattern of HDAC inhibitors and their applications.

Compound	Group	HDAC specificity	FDA approved application	Other applications in malignant tumor	(Refs.)
Vorinostat	Hydroxamate	Class I, II	Cutaneous T cell lymphoma	Pancreatic cancer, neuroblastoma, acute myeloid leukemia, breast, osteosarcoma, pleural mesothelioma and lung cancer	(44)
Panobinostat	Hydroxamate	Class I, II	Multiple myeloma	Non-small cell lung cancer, diffuse intrinsic pontine glioma, acute myeloid leukemia, glioblastoma, anaplastic glioma, pancreatic and colon cancer	(45)
Trichostatin A	Hydroxamate	Class I, II	None	Gastric cancer, chondrosarcoma, bladder, esophageal and breast cancer	(46)
Dacinostat	Hydroxamate	Class I, II	None	Acute myeloid leukemia	(47)
Tubacin	Hydroxamate	Class IIb	None	Burkitt's lymphoma, neuroblastoma, urothelial cancer, acute lymphoblastic leukemia and breast cancer	(48)
Belinostat	Hydroxamate	Class I, IIb	Peripheral T Cell Lymphoma	Cancer of unknown primary site, renal cancer, cutaneous T-cell lymphoma, thymic epithelial tumor and acute myeloid leukemia	(49)
Romidepsin	Cyclic tetrapeptide	Class I	Cutaneous T cell lymphoma; T-cell lymphoma	Anaplastic glioma, renal, colon, prostate small-cell lung, head and neck and gastric cancer	(50)
Entinostat	Benzamide	Class I	None	Breast cancer, lung cancer, B-cell lymphoma, acute myeloid leukemia, myelodysplastic syndrome and hepatocellular cancer	(51)
Valproic acid	Short-chain fatty acid	Class I, IIa	None	Acute myeloid leukemia, primary chronic lymphocytic leukemia, gastric, pancreatic, ovarian and renal cancer	(52)
Sodium 4-phenyl-butyrate	Short-chain fatty acid	Class I, IIa	None	Bladder, breast and colon cancer and Burkitt's lymphoma	(53)
Trifluoromethylketone	Electrophilic ketones	Class II	None	Hepatocellular cancer and neuroblastoma	(54)
Mocetinostat	Miscellaneous compounds	Class I	None	Pancreatic cancer, B-cell chronic lymphocytic leukemia, small cell lung cancer, colon cancer, multiple myeloma and Hodgkin's lymphoma	(55)
EX-527	Other	Class III	None	Pancreatic cancer, melanoma, hepatocellular, breast and gastric cancer	(56)
Cambinol	Other	Class III	None	Lung, pancreatic, breast, colon cancer and Burkitt's lymphoma	(57)
I-7ab	Other	Class I	None	Prostate cancer and acute myelocytic	(58)
SB939	Other	Class I, II, IV	None	Leukemia, myelofibrosis, ovarian and colon cancer	(59)

HDAC, histone deacetylase; FDA, Food and Drug Administration.

activating mechanisms that induce specific cellular responses to the environment (7).

3. Environment factors and the how to influence epigenetic modifications

Epidemiologically, the majority of environmental factors, including geographical regions, stress, nutrition and toxicants, affect malignant diseases by inducing epigenetic modifications (8). Additionally, the environmental factors include race, climate, life style, diet, nutritional factors (9), airborne polycyclic aromatic hydrocarbons (10), toxicants (e.g., cocaine) (11), alcohol (5), fungicides or pesticides (e.g., dicofol and vinclozolin) (12), aflatoxin (13), bacteria (e.g., *Helicobacter Pylori*), viruses (e.g., hepatitis virus) (14), heavy metal exposure (e.g., cadmium, arsenic) (15) and endocrine disruptors (e.g., bisphenol-A) (16).

Previous studies have demonstrated that the majority of environmental factors have the ability to interfere with DNA methylation by altering the availability of the methyl donor or the activity of DNA methyltransferases (DNMTs) (17). Compounds in the environment, including the endocrine disruptors (e.g., diethylstilbestrol), tobacco and ethanol, may induce epigenetic modification (18). Dysplasia and sudden exposure in the critical stage (e.g., early development) to environmental factors promotes disease occurrence in adults (19). Environmental factors may permanently change the epigenetic genome and gene expression levels, and result in alterations of phenotypes and susceptibility to disease (19).

Evidence from liver cancer tissue samples revealed that ethanol altered the methylation status of histone H3 at two lysine residues (e.g., lys-4/9) and increased the phosphorylation of histone H3 at two serine residues (e.g., ser-10/28) (5). Chronic ethanol uptake may result in upregulation of certain miRNAs (miR-34a, miR-107 and miR-122), which can also alter the methylation pattern of DNA in liver tumors, thereby affecting gene expression levels (20). Taken together, histone modification, DNA methylation and miRNA may produce a synergistic effect in ethanol-associated tumors. It was reported that the hepatitis B virus X protein may induce aberrant epigenetic modifications in human hepatocellular carcinoma by inducing the DNA hypermethylation of tumor suppression genes (21), promotion-associated gene-specific DNA hypomethylation, histone acetylation or deacetylation and alterations of miRNAs (22).

Epigenetic modifications serve an important role in cancer development; the deregulation of this has been identified as a feature of cancer initiation (3). Investigating the underlying mechanisms may aid the development of specific therapeutic targets and personalized epigenetic medicines (23). Epigenetic drugs have emerged as potential agents for cancer treatment (Tables I and II).

4. Epigenetic modifications and inhibitors

Evidence has demonstrated that histone modifications together with DNA methylation constitute an 'epigenetic code', which regulates transcriptional status and disrupts code writing or interpretation (23). These aberrant alterations to the code may activate the expression of oncogenes, including c-Myc,

Table III. Promising epigenetic inhibitors.

Drug	Inhibitor Type	Targets	(Refs.)
BIX-01294	HMT(G9a)	H3K9me2	(59)
UNC0638	HMT(G9a)	H3K9me2	(60)
GSK126	HMT(EZH2)	H3K27	(61)
EPZ5676	HMT(DOT1L)	H3K79	(62)
OG-L002	HMT(LSD1)	MAO-A and B	(63)
ORY-1001	HMT(LSD1)	LSD1	(64)
----	HMT (Jumonji C)	LSD1	(65)

HMT, histone methyltransferases; LSD, lysine-specific demethylase; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; DOT1L, DOT1 like histone lysine methyltransferase.

which promotes the development of specific small molecule modulators of histone binding proteins (24). A few of these compounds have been used in clinical development for tumor therapy, Tables I and II summarized the current reported epigenetic inhibitors.

DNMTs, including DNMT1, DNMT3A and DNMT3B, catalyze a methyl group transformation from the methyl donor S-adenosylmethionine to the C-5 of cytosine in DNA. In malignant cells, hypermethylation at the CpG island induces suppression of numerous vital tumor suppressor genes, including p16 (25). Thus, small molecules targeting DNMTs may potentially reverse epigenetic silencing of cancer suppressor genes in a number of different cancer types. The DNMT inhibitors were used in tumor clinical treatments, including azacitidine, decitabine and SGI-110 (others are presented in Table I and Fig. 1) (26-42). These compounds demonstrated good anti-proliferative effects in various cancer cell lines, including breast, prostate, lung, pancreas, liver and leukemia (23). However, the practical utility in clinics has been limited by systemic toxicity and off-target effects, including in certain heme malignancies.

The other major category is the histone deacetylase (HDACs) inhibitor, which enables the catalysis of N-acetyl residues hydrolysis in histones and activation of histone acetyl transferases. A previous study revealed that HDACs serve roles as crucial mediators in tumor survival and progression (43). A total of four HDAC inhibitors were approved by the Food and Drug Administration (FDA): Vorinostat, belinostat, panobinostat and romidepsin (details are presented in Table II and Fig. 1) (44-58).

Following the development of epigenetic drugs, second-generation epigenetic inhibitors emerged, including histone methyltransferase inhibitors, euchromatic histone lysine methyltransferase 2 (G9a) inhibitors, enhancer of zeste 2 polycomb repressive complex 2 subunit inhibitors, DOT1 like histone lysine methyltransferase inhibitors, histone demethylases and Jumonji C inhibitors (Table III and Fig. 1) (59-64). These epigenetic clinical agents have intrinsically greater binding specificity to their molecular targets and may be developed as drugs for malignant disease.

Valproic acid (VPA; valproate), an acidic chemical compound, was mainly used in the treatment of epilepsy,

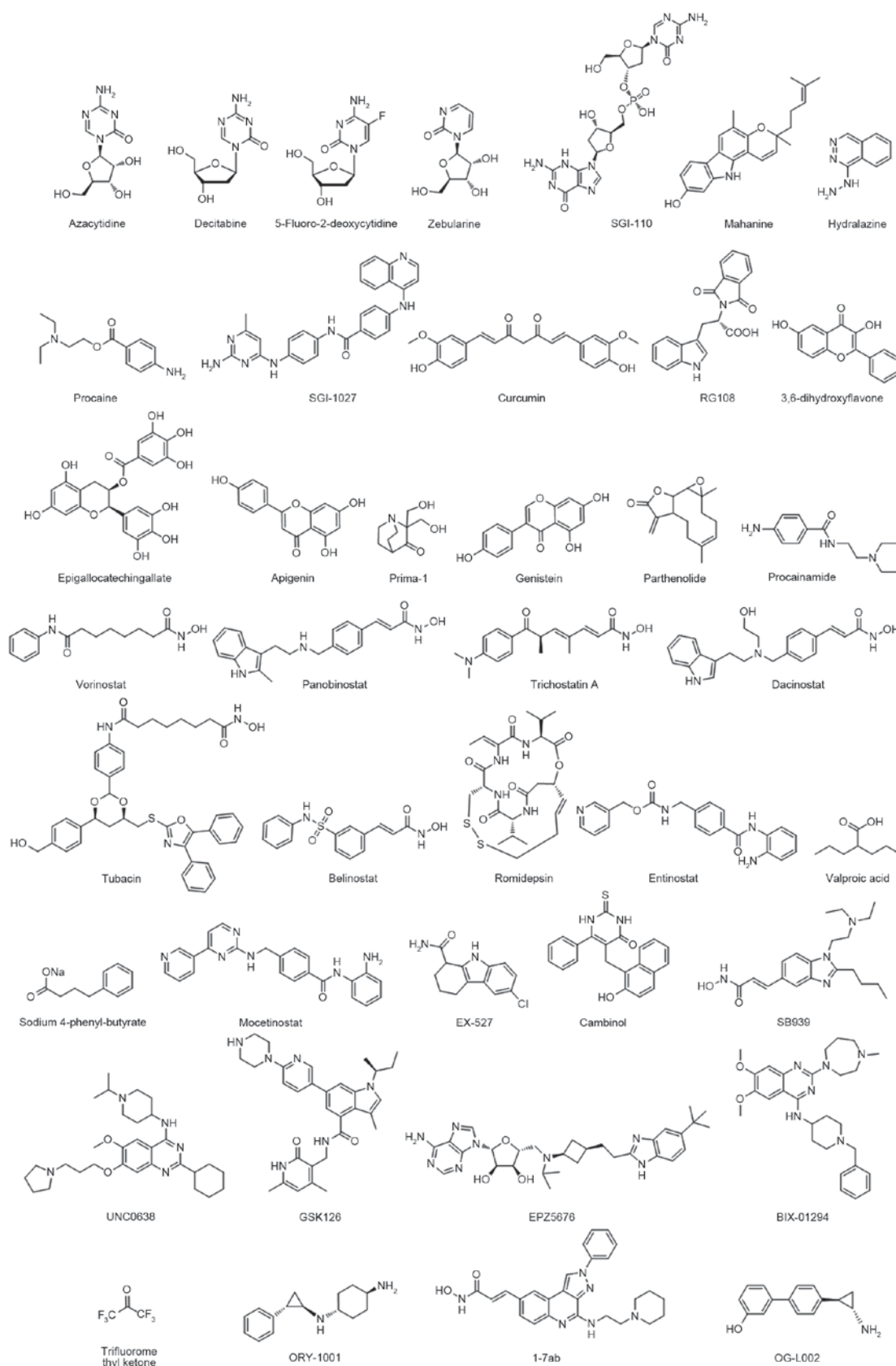


Figure 1. The structural features of promising epigenetic inhibitors.

bipolar mania and migraine prophylaxis previously (65). In 1996, Cinatl *et al* (66), reported the inhibiting effect of VPA on N-myconco protein expression in human neuroblastoma cells, suggesting that VPA may have anticancer properties. In

the past few decades, great effort has been made to study its epigenetic mechanism in various types of cancer, the majority of which focused on transcriptionally activating chromatin structures (67). Recently a phase I/II clinical trial headed by

Iwahashi *et al* (68) demonstrated that S-1 (an oral fluoropyrimidine derivative consisting of the 5-fluorouracil prodrug tegafur combined with VPA for patients with pancreatobiliary tract cancer, had a manageable safety profile and preliminary antitumor activity. Sugimoto *et al* (69), reported that combined VPA with PEG-interferon (IFN)- α increased caspase-3/7 activity, induced IFN- α and - β receptor subunit (IFNAR)1 and IFNAR2 expression and increased the expression levels of IFN- α receptor and IFN regulatory factor 8 in pancreatic cancer, which revealed that VPA may be useful for the treatment of pancreatic cancer via enhancing the function of IFN- α .

5. Novel drug exploration using the old-fashioned 'Drug repositioning' method

Increasing interest has been drawn to the idea of 'drug repositioning'. Although it is a costly approach to novel drug development, the clinical value is low as the majority of the drugs have not passed the phase I trial. Therefore, certain existing drugs have been re-examined (70). A typical and successful example is Viagra, which had high expectations for use in the treatment of cardiovascular disease, but serves a role in the treatment of male sexual dysfunction. Another example is vorinostat, which was initially designed for cutaneous T-cell lymphoma but facilitated a breakthrough in HIV treatment by disturbing HIV's latency in stationary phase patients (71). Due to the potential effects and characteristics of targeted treatment for epigenetic-associated disease, epigenetic drugs are making progress and attracting attention for cancer therapy (72). The FDA approved the aforementioned epigenetic drugs, including the DNMT inhibitors azacitidine and decitabine, which were revealed to be effective in myeloid splastic syndrome therapy (73). The HDAC inhibitors, vorinostat, romidepsin and belinostat, also acquired recognition in the treatment of cutaneous and peripheral T cell lymphoma (74). Emerging evidence demonstrated that azacitidine and decitabine also possessed anticancer effects on liver cancer, pancreatic cancer and breast cancer cells (75). It is reasonable to speculate that combining azacitidine and decitabine with other anticancer drugs, including platinum compounds and monoclonal antibodies may produce a stronger anticancer effect (76). Furthermore, vorinostat and romidepsin were also popular for gastric and lung cancer therapy (77,78). Novel drug development also requires investigation using cutting-edge technology, including gene sequencing.

Sanger sequencing, first-generation sequencing that markedly impacted gene research has now evolved into next generation sequencing (NGS), which has a lower cost, higher speed and improved throughput. Recently, an epigenetic study used NGS and achieved a novel understanding of ependymoma in children. The previous study investigated DNA methylation patterns and defined a tumor CpG island methylator phenotype for infant nervous system malignancy, using whole genome sequencing and whole-exome sequencing (79). They revealed that the development of posterior fossa ependymomas group A (PFA), which had a poor prognosis, occurred primarily in infants and was associated with epigenetic modifications. The PFA exhibits an increased number of methylated CpG sites, an increased number of genes with CpG methylation and an increased number of genes that are

transcriptionally silenced by CpG hypermethylation in tumor development and maintenance. The *in vivo* data demonstrated that treatment with decitabine and Gsk343 is able to attenuate the proliferation of PFA cells. This may further support the concept of 'drug repositioning'. Widely applicable in modern cancer clinical research (80), NGS has begun to elucidate the underlying epigenetic mechanisms; however, there is a large amount of data. Methodological improvement is required for convenient clinical application.

6. Summary

Epigenetics provides a molecular and etiological mechanism for the incidence of malignant cancer. Early ectogenic exposure can program later life physiology and adult onset disease due to the replication of the epigenome during somatic cell mitosis, during which 'epigenetic transgenerational inheritance' initiates. Although an increasing number of approved antitumor drugs have emerged, the outcomes of clinical trials have been unsatisfactory. This may be due to the lack of specificity and the combination with environmental exposure. In view of the critical roles of ectogenic cues on tumorigenesis, comprehensive analysis and treatment is required for early diagnosis, standardized and personalized treatment. The presence of epigenetic factors is associated with gene abnormality in premalignant cancer, and its potential reversibility indicated that epigenetic alterations may be promising biomarkers and potential novel mechanism-based strategies for tumor early diagnosis and treatment.

Previous clinical trials revealed that first generation inhibitors, including DNMTs and HDACs, have been observed to have limited utility due to toxicity and off-target effects. However, second generation compounds have been suggested to have more promise. These clinical agents have greater selectivity for their molecular target and may be a robust driver or key mediator at safe doses in malignancies. Additionally, drug repositioning still requires further enhancement and study. The improvement of epigenetic therapeutic strategies needs to be combined with cytotoxic factors, immunotherapy, targeted kinase inhibitors, NSG and the possible environmental cues.

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