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REVIEW

Epigenetic therapy: use of agents targeting deacetylation and methylation in cancer management

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Abstract: The emergence of epigenetic mechanisms as key regulators of gene expression has led to dramatic advances in understanding cancer biology. Driven by complex layers that include aberrant DNA methylation and histone modification, epigenetic aberrations have emerged as critical processes that disrupt cellular machinery and homeostasis. Recent discoveries have already translated into successful clinical trials and improved patient care, with several agents approved for hematologic disease and others undergoing study. As the field matures, substantial challenges persist that will require resolution. These include the need to decipher more fully the interplay between the epigenetic and genetic machinery, patient selection and improving treatment efficacy in solid tumors, and optimizing combination therapies to counteract chemoresistance and minimize adverse effects. Here, we review recent progress in epigenetic treatments and consider their implications for future cancer therapy.

Keywords: epigenetics, cancer, acetylation, methylation, histone, transcription, tumor

Introduction

The field of epigenetics comprises a wide range of reversible modifications that orchestrate gene expression. The genome is organized into relaxed euchromatin and condensed heterochromatin, and DNA is interlaced among histones, which are in turn post-translationally altered to enable or disable transcription. The relative structural simplicity of DNA is therefore supported by immense modulation from epigenetic factors that are both tissue- and context-specific. It is these factors that enable a broad range of phenotypes to be manifested from a common DNA blueprint.

Advances in deciphering the fundamental machinery of the epigenome have led to significant insights into cell physiology as well as oncogenesis. This information has provided a fuller and more nuanced understanding of epigenetic abnormalities linked to genetic mutations, including the roles of methylation and acetylation. Although these marks are somatically heritable, the fact that they are also reversible suggests exciting implications for therapy. Defining (and restoring) the "normal" epigenetic landscape has consequently been the focus of active investigation, and has already generated breakthroughs in cancer detection, treatment, and prognosis. Swift approval of epigenetically targeted drugs by the US Food and Drug Administration (FDA) for hematologic conditions has cemented its role in the clinical sphere[1–4] (Table 1), and many phase II and III clinical trials are under way for multiple conditions, including solid malignancies.[5–7] Below, we highlight the interface between the genome and epigenome and examine the clinical impact facilitated by current and future epigenetic agents.

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Table 1 Examples of approved epigenetic agents

Agent	Class	Disease indications	FDA approval data	Main study institution	Number of patients	Basis of approval	Side effects
5-azacitidine	DNMT inhibitor	MDS	2004	Memorial Sloan-Kettering; Mount Sinai	191	Phase III trial; 23% response rate; significantly improved median survival compared to supportive care (18 months vs 11 months)	Myelosuppression (thrombocytopenia, neutropenia, anemia)
Decitabine	DNMT inhibitor	MDS	2006	MD Anderson	170	Phase III trial; 17% response rate; trend toward improved median survival compared to supportive care (12 months vs 8 months)	Myelosuppression (thrombocytopenia, neutropenia, anemia)
Vorinostat	HDAC inhibitor	CTCL	2006	Duke	74	Phase IIB trial; 30% response rate; median time to progression was 5 months	Diarrhea, fatigue, nausea, anorexia
Romidepsin	HDAC inhibitor	CTCL	2009	National Institutes of Health; King's College London	167 (96 + 71)	Phase II trails; 34%–38% response rates; median response duration was 11–15 months	Nausea, fatigue, anemia, thrombocytopenia, ECG T- wave changes, neutropenia, and lymphopenia

Abbreviations: DNMT, DNA methyltransferase; HDAC, histone deacetylase; MDS, myelodysplastic syndrome; CTCL, cutaneous T-cell lymphoma.

DNA methylation and histone modification

Two of the most common types of epigenetic alterations in cancer involve aberrant changes in DNA methylation and histone modification. These alterations occur at multiple layers of regulation, directing gene expression via maintenance of restricted and permissive chromatin states. Such regulators can also be commandeered by cancer cells for oncogenic gain.[8] Methylation consists of the addition of a methyl group to the 5′ position of the cytosine ring in CpG dinucleotides (5 mc) and typically occurs in CpG islands within promoter regions. DNA hypermethylation in promoters can lead to the silencing of gene expression. Other areas found to harbor CpG methylation include vast areas in the genome with repetitive sequence, such as centromeres and transposon elements (involved in chromosomal stability),[9] CpG island shores,[10] noncoding regions (ie, enhancer regions and miRNAs),[11] and gene bodies (silencing alternative transcription start sites).[12] Approximately 60% of gene promoters contain CpG sites.[13]

The central workhorse molecules that lay down DNA methylation are the DNA methyltransferases. As a maintenance enzyme, DNMT1 preserves existing methylation patterns after cell replication, and its deletion leads to apoptosis[13] as well as death in mice if lost during embryonic development.[14] In contrast, DNMT3 A and -3B are de novo methyltransferases that methylate previously unmethylated DNA. While they are in the same general class of enzymes and share similarities within their catalytic domains, their roles in tumorigenesis may differ: DNMT3A deletion may promote cancer progression,[15] yet DNMT3B deletion may in fact inhibit oncogenesis by liberating previously silenced tumor-suppressor genes.[16,17] Interestingly, a substantial degree of DNA methylation in embryonic stem cells appears to occur independently of CpG sites,[18] and the Ten-Eleven-Translocation (TET) oxidase family has been reported to convert 5-methylcytosine to 5-hydroxymethylcytosine as a step toward demethylation, a process that does not seem to be restricted to CpG islands.[19] The exact roles of these phenomena in epigenetic regulation remain to be elucidated.

Besides direct manipulation of DNA, modification of the core histones (ie, two copies of H2A, H2B, H3, and H4 proteins) also play important roles in epigenetic regulation. These histones selectively bind and release DNA as nucleosomes to moderate transcription, a process that is regulated through the addition of acetyl, methyl, phosphoryl, ubiquityl, or sumoyl groups, producing a dynamic epigenetic histone code (Figure 1).[20] These histone marks are deposited or removed by a plethora of proteins and clinical targets, including histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), histone demethylases (HDMs), kinases, phosphatases, and others. Here, we will summarize some salient parts of this biology, and for greater detail, the reader is directed to a couple of excellent reviews on these processes.[21,22] Acetylation of lysines at specific sites (such as on H3K4, etc) by HATs negates the positive histone charge, permitting

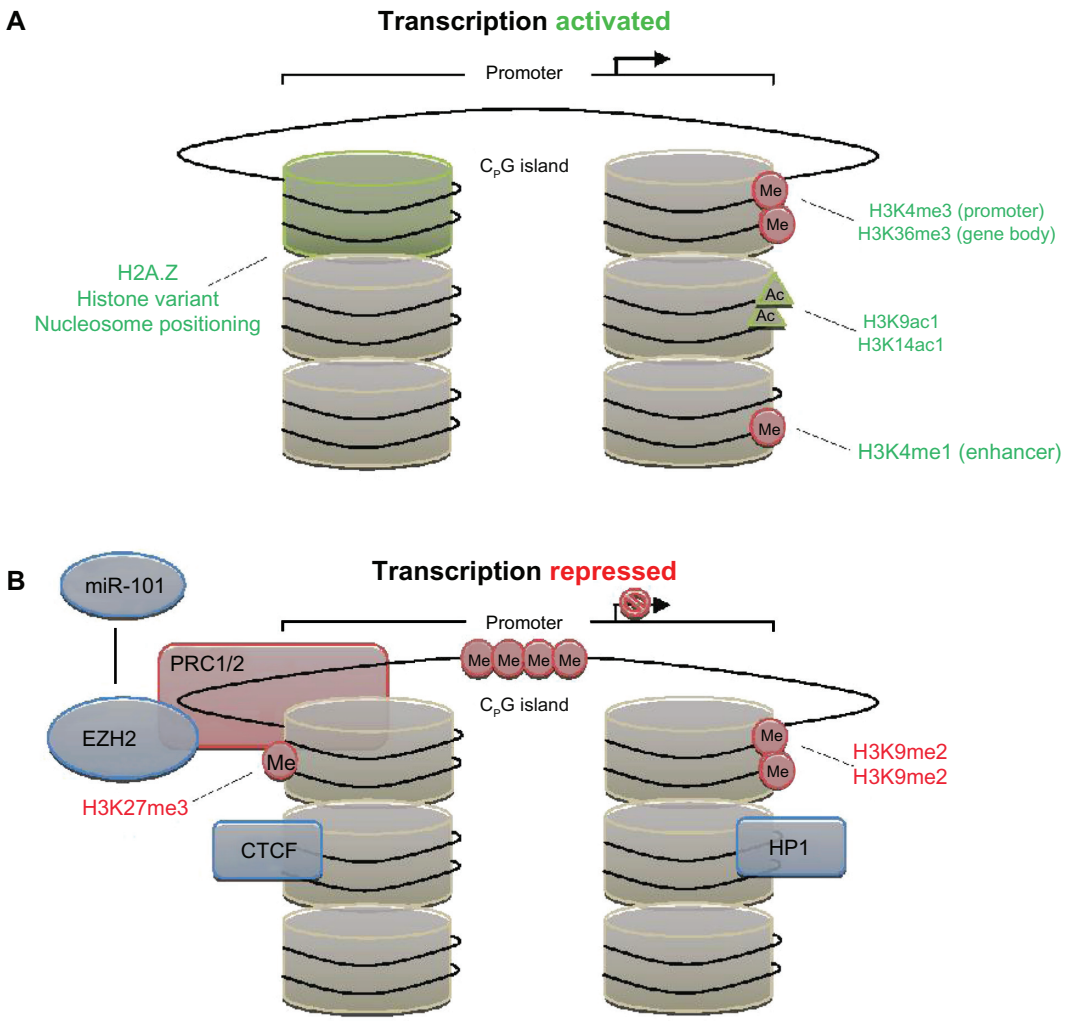


Figure 1 (**A** and **B**) Epigenetic mechanisms of transcriptional regulation. (**A**) Transcriptional activation, and (**B**) transcriptional repression with associated histone marks.
Abbreviations: EZH2, enhancer of zeste 2; PRC1/2, polycomb repressive complex 1/2; CTCF, CCCTC-binding factor; Me, methylation mark; Ac, acetylation mark.

negatively charged DNA to take on a transcription-ready configuration. HDACs, however, remove acetyl groups from histones, causing the oppositely charged histone to bind DNA and shield it from expression. While there are exceptions to each generality, DNA methylation typically silences gene expression, while histone marks can activate or silence genes, depending on the target residues, the targeted histone and extent of the alteration.[23]

Histone marks work together. Numerous histone modifications are now known to synergize in a combinatorial way, establishing specific states to activate or inhibit expression. Permissive chromatin states, for instance, are established by histone H3 marks such as trimethylation of lysine (K) 4 over the promoter and K36 over the gene body (H3K4me3 and H3K36me3, respectively).[24,25] Other enabling marks include monoacetylation of H3K9 and H3K14 (H3K9ac1 and H3K14ac1),[26] the presence of variant histones such as H2A.Z,[27] and methylation of enhancer elements downstream (H3K4me1).[28] Nucleosome positioning represents an additional contributory layer, and is determined by the intrinsic binding affinity of the DNA sequence, competitive binding of surrounding proteins, and translocation activity by adenosine triphosphate-dependent remodeling complexes.[29]

Conversely, heterochromatin configurations that compact nucleosomes are classically indicated by H3K27me3, H3K9me3, and H3K9me2,[30] as well as the presence of inhibitory proteins such as CTCF and HP1.[31,32] This is in addition to dense, localized DNA methylation. Repression can be initiated by the Polycomb group (Polycomb repression complex [PRC]) proteins, which methylate the histones in promoter regions.[33] Such PRC regulators, including enhancer of zeste 2 (EZH2),[34] are themselves regulated by noncoding RNAs such as miRNA-101 to inhibit expression.[35,36]

Collectively, such interplay between systems previously thought to be independent underscores the overarching importance of the epigenome in coordinating transcription, and of course downstream biological events. Its complexity gives rise to enormously flexible conditions that guide development and physiology, but can also be readily misappropriated for disease states such as tumorigenesis.

Epigenetic mechanisms of transcription regulation in cancer

Epigenetic dysregulation in malignant cells can be generalized across cancer types, and is characterized by global hypomethylation and focal hypermethylation.[37] These events occur early on in tumorigenesis, including in early stage and in situ lesions,[38] suggesting that these changes help establish an advantageous milieu for cancer formation. Such broad hypomethylation has been shown to induce genomic instability by activating normally quiet transcription start sites and transposon activity (increasing the likelihood of structural variation),[20,37] while aberrantly methylated promoter areas silence key tumor suppressors. Similar studies have reported decreased acetylation from overexpressed HDACs and inhibited HATs (eg, H4K16ac1),[39] as well as dysregulated histone methylation (eg, H4K20me3).[40] Together with genetic mutations, epigenetic changes can engender favorable environments for tumorigenesis and resistance to therapy. Moreover, epigenetic alterations leading to cancer are not limited to just direct change of gene function, but also predispose to genetic mutation or dysregulation of entire signaling pathways and DNA integrity.[41] Genetic driver mutations affecting epigenetic players such as DNMT3A, UTX, etc[42] have been reported to be quite frequent events.[43]

Aberrant promoter hypermethylation is a hallmark of cancer and is one of the most common alterations seen in malignancies. VHL1 (renal carcinoma), BRCA1 (breast cancer), and RB1 are examples of classic tumor suppressors whose dysregulation can result from either mutation or epigenetic silencing via hypermethylation.[44] Other tumor suppressors that are mutated (ie, CDKN2A, encoding INK4A) can instead be inactivated by epigenetic silencing.[45,46] This was first seen years ago in a number of ad hoc analyses on candidate cancer genes.[47] These findings have been confirmed through high-throughput, global analyses of cancer genomes and epigenomes, which for any given cancer gene may show an absence of genetic mutations, yet reveal epigenetic-based deregulation instead.[48–51]

Other epigenetic abnormalities involve regulatory mechanisms only recently discovered. As described above, TET proteins add hydroxyl groups to 5 mC and not only initiate demethylation but also protect against unsolicited methylation. TET proteins have been found to compete with IDH1 for a common cofactor (α-ketoglutarate), which mutant IDH1 uses to produce the 2-hydroxyglutarate metabolite.[52] This byproduct inhibits TET2, thereby incapacitating the TET-dependent hydroxylating system and allowing methylation to accumulate in IDH1-mutated cancers. This process may contribute to the glioma CpG island methylator phenotype,[53] which characterizes GBM subtypes with distinct clinical and molecular features.[54] Interestingly, CpG island methylator phenotype-positive phenotypes appear to have better prognosis in brain and breast cancers.[54–56] TET alterations observed in cancer include fusion transcripts (ie, MLL-TET1) as well as inactivating mutations and deletions at the TET2 locus.[57]

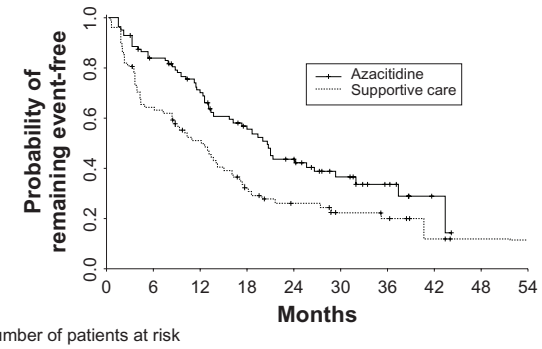
Similarly, dysregulation or reprogramming of histone modifications has been observed in cancer. Viral protein binding of transcriptional regulators such as CREBBP/EP300 has been shown to induce hypoacetylation (H3 K18ac1) and subsequent transformation,[58,59] while global overexpression of the HDAC family has been demonstrated across multiple tumor types.[39] Moreover, EZH2, a major HMT of the PcG system, is often overexpressed in cancer.[60,61] The ensuing aberrant silencing of tumor-suppressor genes strongly implicates a causative oncogenic role for PcG complexes. It appears that as more mechanisms of epigenetic regulation are uncovered, so too are additional means for dysregulation and oncogenesis.

Epigenetic alterations may serve as useful biomarkers for detecting disease and predicting therapeutic efficacy. For example, hypermethylation of GSTP1 (a glutathione *S*-transferase) is found in approximately 85% of prostate cancer, including prostate intraepithelial neoplasia.[62] This is not the case in benign hyperplastic prostate tissue, and therefore its detection in blood or biopsied tissue can be used to detect the presence of prostate cancer cells.[63,64] Similarly, MGMT and MLH1 (DNA mismatch-repair genes) have been demonstrated to undergo epigenetic inactivation in gliomas[65] and ovarian cancers,[66] respectively. Though this may facilitate oncogenesis, it can also prevent such malignancies from recovering from DNA damage caused by chemotherapeutic agents. Patients with hypermethylated MGMT or MLH1 phenotypes have accordingly been shown to have superior clinical responses following treatment with certain cytotoxic agents.[67]

Normal cells may employ alternative repair schemes to recover in ways that cancer cells cannot.

The clinical utility of epigenetic agents in cancer management

The malleable and reversible nature of the cancer epigenome presents intriguing opportunities for novel treatments. Several drugs (specifically DNMT and HDAC inhibitors) have already been approved for select indications, and research efforts have resulted in the development of new drugs designed to be more selective and less toxic. Discovery of how tumors adapt epigenetic machinery to their advantage has also improved understanding of how cancers develop chemoresistance to existing drugs. As such, sensitizing resistant tumors with epigenetic agents to restore the impact of conventional drugs has become a major area of investigation.



Number of patients at risk

Azacitidine	89	69	55	39	28	16	9	2	0	0
Observation	82	51	38	22	15	10	8	3	1	1

Figure 2 Kaplan–Meier curves from a trial of azacitidine in patients with myelodysplastic syndrome.

Note: Plot shows time to acute myeloid leukemia transformation or death.

Adapted with permission. © 2002. American Society of Clinical Oncology. All rights reserved. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429–2440.[71]

Targeting DNA methylation

DNA methyltransferase inhibitors have found the earliest and greatest success as prototypical epigenetic agents. Azacitidine and decitabine were FDA-approved in the mid-2000s for treatment of myelodysplastic syndrome (MDS). As nucleoside analogues, they replace cytosine during DNA replication, in the process trapping DNMTs and targeting them for degradation. Despite indiscriminately targeting DNMTs,[68] they were found at low dosages to selectively reactivate gene expression with relatively few side effects.[69]

Landmark phase III trials with MDS patients comparing decitabine or azacitidine with placebo found a response rate up to 30% that was relatively durable (decitabine, median 10.3 months), including 9% demonstrating a complete response (Figure 2).[70,71] Compared to supportive-care patients, however, those treated with decitabine did not have significantly improved delayed time to acute myeloid leukemia (AML) transformation or death. More recent phase III trials analyzing azacitidine for higher-risk or elderly MDS patients, however, have demonstrated improved overall survival.[72] Besides MDS, DNA methyltransferase inhibitors have also shown some utility for AML. Decitabine, in a number of phase II trials, showed complete responses in 24%–52% of patients, with pronounced benefit for older patients.[73,74] The main documented toxicities were myelosuppression (including neutropenia and thrombocytopenia), as well as nausea and vomiting.

That a substantial portion of patients benefited to some degree from such demethylating agents, which are quite nonspecific, is somewhat surprising. There is clearly room to improve the efficacy of this class of drug, which will require intensive investigation. Potential avenues for improvement include determining the optimal duration of treatment needed and deducing azacitidine's and decitabine's most important molecular effects (key effector genes).[69] Other priorities include minimizing side effects. Two newer DNMT inhibitors include S110, which releases decitabine intracellularly,[75] and CP-4200, a derivative of azacitidine with an elaidic acid modification,[76] have both shown relatively more potent tumoricidal activity in cell lines and mouse models and await clinical investigation. Nanaomycin A, one of the first DNMT3B-specific inhibitors, has been shown to reactivate silenced tumor-suppressor genes.[77] Results from clinical trials will be needed to determine what incremental benefit, if any, these novel compounds will provide.

Targeting histone acetylation/deacetylation

By restoring acetylation to lysine residues on histone tails, HDAC inhibitors counteract the global overexpression of HDACs in cancer and reinstate a more permissive nucleosome structure for transcription. Inhibitors typically target the zinc-dependent active sites of HDACs, with the exception of class III HDACs (sirtuins), which are NAD^+-dependent and do not primarily act on histones.[20,78] The effects of HDAC inhibitors appear to be to promote G_1 or G_2/M cell-cycle arrest, as well as apoptosis and cell differentiation. Intriguingly, the basis of their efficacy (and toxicity) may not only be limited to histone modification: other reported HDAC targets include p53, signal transducer and activator of transcription 3, heat shock protein 90, and other important proteins and changing the acetylation status of these may contribute to the biological effects observed.[79]

Although there are numerous structural classes of HDAC inhibitors, they can be stratified into broad HDAC inhibitors and class-specific agents. Vorinostat (a pan-HDAC inhibitor) and romidepsin (a class I HDAC inhibitor) have each shown > 30% response rates against cutaneous T-cell lymphoma (CTCL) in phase II trials[1–4] (Figure 3), and accordingly were approved for use by the FDA in the late 2000s. Significant adverse events noted were diarrhea, hypercholesterolemia, and anemia for vorinostat, and nausea, cardiotoxicity, and fatigue for romidepsin.[79,80] Though generally more tolerable than conventional chemotherapeutic agents, fatigue has been severe enough to cause discontinuation of HDAC inhibitors in up to 30% of patients.

Nonetheless, enthusiasm continues to build for this class of drug, with more agents in development and undergoing trial than any other class of epigenetic drug. Panobinostat, another pan-HDAC inhibitor, is currently under investigation for numerous hematologic malignancies. A recently reported phase II trial for refractory Hodgkin's lymphoma in 129 patients showed tumor reductions in 74%, with a median duration of response of 6.9 months.[81] A phase III trial with panobinostat and bortezomib is underway for multiple myeloma patients.[69] Similarly, the multiclass specific HDAC inhibitor mocetinostat (class I and IV) has been studied in phase II trials for refractory Hodgkin's lymphoma, refractory diffuse large B-cell lymphoma, and follicular lymphoma.[79,82–84] Encouraging results have been seen on preliminary analysis that appear to indicate promise, including a 38% response rate for Hodgkin's lymphoma patients.[82] Finally, preclinical studies show potential for novel compounds such as JQ1 and I-BET, which inhibit bromodomain (BRD)-containing proteins. BRD4, for instance, can bind acetylated histones, leading to proliferation and overexpression by recruitment of the P-TEFb complex or myc.[85] While known HDAC inhibitors can restore this acetylation, novel compounds such as JQ1 are potentially more specific, as they block contact between BRDs and acetylated histones.[86] Another synthetic drug called I-BET has also been shown to bind and neutralize the active BRD pocket, competitively reducing BRD4's sequestering activity.[87] These two drugs demonstrate that targeting transcription factors and epigenetic readers can be a potentially promising avenue to explore.

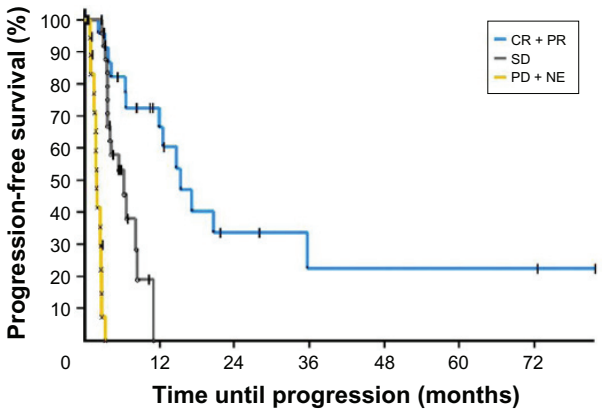


Figure 3 Kaplan–Meier curves from a phase II trial of romidepsin in patients with cutaneous T-cell lymphoma showing progression-free survival of patients with complete response (CR) or partial response (PR), patients with stable disease (SD), and patients with progressive disease (PD) or nonevaluable (NE) patients.
Note: Adapted with permission. © 2009. American Society of Clinical Oncology. All rights reserved. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol.* 2009;27(32): 5410–5417.[4]

Paradoxically, HAT inhibitors have also been shown to have some antitumor activity. This contrasts with the global hypoacetylation already seen in many cancers. Naturally occurring drugs such as curcumin, garcinol, and anacardic acid appear to selectively inhibit EP300, CREBBP, or KAT2B, leading to apoptosis or sensitization to therapies such as radiation.[88–90] As no clinical trials have yet been completed, this class of agents remains largely investigational.

Histone methylation/demethylation

In contrast to the more global activity of histone acetylation enzymes, HMTs and HDMs can be somewhat more discriminating in the specific amino acid residues they target.[84,91] This has exciting therapeutic implications, given that elimination of select histone marks could enable more tailored treatment while potentially minimizing side effects. Yet despite the promising nature of these targets, only a few clinically viable compounds have been identified so far, and all currently remain in preclinical levels of study.

Among the first histone demethylases identified was lysine-specific demethylase 1 (LSD1, or KDM1), a flavin adenine dinucleotide-dependent amino oxidase.[92] By targeting H3K4me1 and H3K4me2, LSD1 selectively mediates repression and has been found to be overexpressed in a significant number of cancers, including tumors of the brain, breast, and prostate, thereby making it an attractive target for drug therapy.[92–94] Small molecules such as SL11144 and tranylcypromine appear to be potent inhibitors of LSD1,[95,96] and have been shown in cancer cell lines to restore expression of multiple aberrantly silenced tumor suppressors, including secreted frizzled-related protein and GATA transcription factors. Research with neuroblastoma xenografts also demonstrates antitumor activity.[94] However, similar to HDACs, off-target effects on H3K9me2 and

DNMT1 limit its immediate usefulness,[97] and further study is needed.

The previously mentioned Polycomb group genes also are undergoing active investigation as potential targets. The PRC1 and PRC2 complexes are responsible for H3K27me3-mediated repression of transcription.[98] Such histone marks can lead to DNA methylation and sustained gene silencing. EZH2, a member of the PRC2 complex, is another attractive drug target, given its overexpression in head and neck, breast, and prostate cancers,[99] and is targeted by a hydrolase inhibitor called 3-deazaneplanocin A (DZNep). By countering EZH2 and inhibiting H3K27 trimethylation, DZNep has been shown to induce differentiation as well as apoptosis in cancer cell lines and xenografts,[100,101] while sparing normal cells. This apparently selective reversal of PRC2-mediated gene repression constitutes a novel treatment approach, and results from clinical trials are forthcoming. However, cancer-mutation surveys have shown that EZH2 can act as an oncogene in some cancers, but as a tumor suppressor in others. Therefore, use of EZH2 inhibitors in the clinic can only be implemented after judicious study.

Future developments in epigenetic therapy

Epigenetically targeted drugs have already become an important part of the clinical armamentarium, and in some refractory conditions are the only drugs with any activity available to patients. Yet initial successes notwithstanding, challenges remain that must be addressed by future studies. These issues involve expanding the therapeutic reach beyond hematologic cancers, identifying the synergistic potential of combination therapy for better patient outcomes, and understanding the mechanistic basis of these agents to narrow drug activity and more precisely target aberrant marks.

One of the main criticisms of epigenetic therapy has been its relatively lower efficacies when tested on solid tumors.[79,84] This is likely due to the heterogeneity of solid tumor cells, which may make it more difficult for agents to penetrate and less difficult for tumors to develop resistance. This is especially telling with the epigenetic agents already approved for hematologic malignancies like MDS and CTCL. Vorinostat has been tested as a single agent in head and neck, breast, colorectal, and prostate cancer trials,[102–104] and has not shown efficacy. A phase II trial with 94 non-small-cell lung cancer patients did not show significantly improved progression-free or overall survival, with 41% of patients unable to complete the six-cycle regimen.[105] Similarly, phase I and II trials testing romidepsin (approved for CTCL) showed very marginal clinical improvement when treating refractory solid malignancies, including kidney, prostate, and lung.[5,6,106] Unfortunately, testing epigenetic agents against refractory tumors that have become resistant to other first-line therapies increases the likelihood of failure. Furthermore, it will be important to properly select patients using molecular criteria in future trials, as these features are likely to influence heavily the likelihood of response.

Future trials will likely test combination therapies, with the hypothesis that epigenetic agents may enhance sensitivity to conventional drugs (eg, platinum or taxane chemotherapy) that have known activity. By relaxing chromatin with HDAC inhibitors, it is believed that strands are better exposed to DNA intercalation or genotoxic damage.[84] Such synergistic combinations are also under intense study to demonstrate reversal of chemoresistance due to epigenetic adaptation, crucial for treating disease that is recurrent or refractory to first-line treatment. Other strategies are examining the role of dual epigenetic therapies, such as DNMT inhibitors with HDAC inhibitors.[107,108] Given previous experience with azacitidine, it will be essential to master the optimal timing (ie, sequential versus simultaneous) and dosage needed for these cocktails to be effective.

Finally, the advent of next-generation sequencing technologies has made high-throughput mutational and epigenetic analysis accessible and will ultimately allow investigators to paint a more comprehensive portrait of the determinants of response to epigenetically targeted therapies. This will greatly assist in deciphering the many nonhistone and nonpromoter effects observed in many epigenetic agents, including interactivity with miRNAs and kinases. Such large-scale analyses are already under way in mapping cancer genomes via the Cancer Genome Atlas and the International Cancer Genome Consortium. CHIP-seq, whole genome/exome sequencing, RNA-seq, and reverse-phase protein arrays, as well as the bioinformatic expertise necessary to synthesize them, have all helped make rapid strides possible.[109–111] Epigenetic analyses of tumors have already demonstrated clinical utility, as demonstrated by the prognostic and predictive use of MGMT methylation status in GBM.[112] These new tools should lead to substantial improvements in finding reliable biomarkers and selecting the right drugs for the right patient.

Conclusion

With more than 100 epigenetic agents currently under investigation and a handful already approved in the last decade alone, it is clear that epigenetic therapy will continue

to impact the management of cancer patients significantly. Such agents are unlikely to be a universal remedy, but their potential to prolong meaningful life and originate new avenues of treatment remains tantalizing. Much remains to be defined about the epigenome regarding its role and its dysregulation in cancer. The widespread presence of mutations in epigenetic regulators in human cancers suggests that the continued efforts in developing strategies to target epigenetic aberrations may contribute to improving efficacy of cancer management.

Disclosure

The authors report no conflicts of interest in this work.

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