Emerging Epigenetic Targets and Therapies in Cancer Medicine

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ABSTRACT

Abnormalities in the epigenetic regulation of chromatin structure and function can lead to aberrant gene expression and cancer development. Consequently, epigenetic therapies aim to restore normal chromatin modification patterns through the inhibition of various components of the epigenetic machinery. Histone deacetylase and DNA methyltransferase inhibitors represent the first putative epigenetic therapies; however, these agents have pleiotropic effects and it remains unclear how they lead to therapeutic responses. More recently, drugs that inhibit histone methyltransferases were developed, perhaps representing more specific agents. We review emerging epigenetic targets in cancer and present recent models of promising epigenetic therapies.

Significance: The use of DNA methyltransferase and histone deacetylase inhibitors in patients has validated the use of drugs targeted to epigenetic enzymes and strengthened the need for development of additional therapies. In this review, we summarize recently discovered epigenetic abnormalities, their implications for cancer, and the approaches taken for discovering small-molecule inhibitors targeting various properties of the epigenetic machinery. Cancer Discov; 2(5):405–13. ©2012 AACR.

INTRODUCTION

Cells in an organism, regardless of their function, contain identical genetic material yet vary greatly in gene expression and phenotype. Gene transcription is controlled in part through the architecture of its chromatin and through recruitment of transcription factors to specific regulatory elements. These mechanisms are regulated through covalent modifications of DNA and histone proteins that leave the underlying DNA sequence unaltered. DNA methylation at the cytosine of the CpG dinucleotide is associated with gene silencing. CpG is underrepresented in the genome but at the cytosine of the CpG dinucleotide is associated with gene silencing. CpG islands become hypermethylated in cancer, flagging in the recruitment of gene-silencing complexes.

Posttranslational modifications of histone proteins are mediated by enzymes that can add or subtract covalent attachments at specific residues. Histones can be methylated, acetylated, phosphorylated, or ubiquitinated and, depending on the residue being modified, identical chemical modifications can have opposing consequences. In addition, certain histone modifications are dependent on each other and can be found simultaneously on the same genomic loci under appropriate conditions, whereas others are mutually exclusive. Adding another layer of complexity, histone lysine residues can be mono-, di-, or trimethylated, whereas arginines can be monomethylated or symmetrically or asymmetrically dimethylated with each modification having a specific biologic effect. Collectively, the combination of covalent modifications (often referred to as a “histone code”) in cooperation with DNA methylation affects the structural state of chromatin and transcriptional status of a gene. The histone code is “read” by modules found within chromatin regulators including bromodomain, chromodomain, and Tudor domain. Often, an enzyme that creates a specific histone modification contains a domain that recognizes that same modification to spread across a locus.

Increasing evidence links mutations, amplifications, deletions, and rearrangements of genes encoding epigenetic regulators to cancer. Depending on the enzyme involved and the pathways affected, such alterations may lead to changes in gene expression and/or global changes in chromatin structure and function. Epigenetic effects can phenocopy loss of function gene mutation. Increased DNA methylation and repressive histone marks on a promoter silence gene transcription. Conversely, loss of DNA methylation and accumulation of activating marks can, similarly to chromosomal translocation or gene amplification, increase gene expression. Unlike genetic events, epigenetic changes can in theory be

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DOT1L (KMT4)

DOT1L is a unique HMT that has an AdoMet binding motif, similar to those of arginine methyltransferases (1). Additionally, although most histone modifications occur on the N-terminal tails, DOT1L methylates lysine 79 on histone H3 (H3K79) within the globular histone domain on which DNA is wrapped. Furthermore, after monomethylation of lysine 79, DOT1L must dissociate and reassociate with histone for further methylation of the same residue. These unique properties and the fact that DOT1L is the only known H3K79 methyltransferase make DOT1L an attractive target for specific malignancies. DOT1L is expressed throughout embryogenesis and in adult tissues. Its knockout in mice leads to defective angiogenesis in the yolk sac and embryonic death (2). Loss of Dot1l leads to disruption of centromeres and telomeres, suggesting that it is critical for the establishment or maintenance of heterochromatin structures (2). The majority of genes affected by the loss of Dot1l were activated, suggesting that H3K79 methylation by Dot1l played a role in transcriptional repression (3). This contrasts with genome-wide studies showing that actively transcribed genes are enriched for H3K79 methylation (4, 5). Furthermore, DOT1L is associated with the RNA polymerase II elongating complex, supporting the notion that DOT1L promotes gene expression (6).

DOT1L has an important role in aberrant gene regulation mediated by MLL (Mixed Lineage Leukemia/KMT2A) in leukemia. MLL translocations are found in greater than 70% of infant leukemia and 10% of adult acute myeloid leukemia (AML), resulting in fusion of MLL to one of more than 70 different partners and deregulation of MLL target genes (7). MLL is a HMT specific for H3K4, a mark found at the promoters of active loci (5, 8). In leukemia, the gene-targeting domains of MLL are retained in the fusion protein, whereas the C-terminal SET domain is lost, suggesting that aberrant gene activation is not linked to methylation by MLL. Many MLL fusion partners are part of a large multiprotein super elongation complex whose function of promoting transcription possibly plays a role in leukemogenesis (9). Other MLL fusion partners, including the most common translocation partners AF4 and AF9, can recruit a smaller protein complex that includes DOT1L methyltransferase (6). MLL-AF fusion proteins bind to specific targets such as HOX genes, resulting in the recruitment of additional DOT1L, enhanced H3K79 methylation, and transcription. The importance of DOT1L for this process was highlighted by the fact that MLL-AF9 cannot immortalize bone marrow progenitors from Dot1l-null mice (10). Furthermore, elimination of Dot1l expression in MLL-AF9-transformed cells decreased expression of genes bound by MLL-AF9 but not other genes enriched for H3K79 methylation (11). These data suggested that targeting DOT1L might specifically affect leukemia-associated gene activation while sparing normal gene expression.

Using the chemical structure of AdoMet, an obligatory HMT cofactor, as the starting point for the synthesis of candidates, Daigle and colleagues (12) identified EPZ004777 as a potent DOT1L inhibitor (Fig. 1A). Despite its similarity to SAM, EPZ004777 shows remarkable selectivity for DOT1L in vitro and does not affect methylation by other HMTs such as EZH2 (KMT6), SET7 (KMT7), and WHSC1.
cancers, including advanced-stage and high-grade prostate, breast, and lung tumors (15). EZH2 and PRC2 are critical for the control of gene expression in embryonic stem cells, maintaining self-renewal while inhibiting differentiation (16), and these properties of EZH2 appear active when the gene is overexpressed in tumors. EZH2 overexpression induces cell migration and colony formation and induces genomic instability by repression of regulators of DNA repair (17). Conversely, EZH2 depletion suppresses proliferation and attenuates tumor formation in vivo (18). A homologous polypeptide, EZH1, can also form a PRC2-like complex and may have overlapping or complementary roles to those of EZH2 (19). However, the exact interplay between EZH2 and EZH1 is insufficiently understood and it is unclear how this relationship may be affected in cancer.

Recently, somatic mutations and deletions of EZH2 were identified in hematologic malignancies, leading to the gain or loss of EZH2 function. Approximately 30% of diffuse large B-cell lymphomas (DLBCL) and 10% of follicular lymphomas contain a mutation at tyrosine 641 (Y641) within the SET domain, predicted to alter the substrate recognition pocket within the enzyme (20). These mutations are always heterozygous, suggesting that they are either dominant to or cooperate with the wild-type (WT) EZH2 protein. Enzymatic studies showed that WT EZH2 converted unmethylated H3K27 to H3K27me1 and to a lesser extent the me2 and me3 states (21). By contrast, EZH2Y641X failed to recognize unmethylated H3K27 but readily converted H3K27me1 (created by WT EZH2) to H3K27me2 or me3. Accordingly, DLBCL cells harboring EZH2Y641X display increased levels of H3K27me3 (Fig. 1B). EZH2 is silenced in resting, mature B cells and is transiently upregulated in germinal center B cells, where, along with BCL6, it blocks DNA damage response pathways allowing cells to survive the somatic hypermutation of antibody maturation (22). By amplifying these functions and targeting additional pathways, EZH2 mutations may stimulate malignant transformation.

In myeloid neoplasia, EZH2 is most often affected by deletions and nonsense mutations that yield loss of function, and leukemia cell lines harboring EZH2 mutations show decreased H3K27 methylation (23). The presence of activating and inactivating EZH2 mutations in different cancers suggest a complex, context-dependent role of Polycomb proteins in oncogenesis. It is unclear whether EZH2 affects different sets of genes in different malignancies or whether global histone changes may interfere with other chromatin functions such as replication and DNA repair. Nevertheless, the frequent occurrence of genetic lesions affecting H3K27 (Fig. 1B) suggests that this mark is under tight control, which may present a challenge in the design of safe and effective EZH2 inhibitors. The S-adenosylhomocysteine (SAH) hydrolase inhibitor 3-Deazaneplanocin A (DZNεP) is the only EZH2 inhibitor described to date (24). DZNεP can inhibit HMTs by increasing SAH levels, inducing the degradation of EZH2 and leading to a global decrease of H3K27 methylation accompanied by apoptosis of cancer cells. However, in some cells, DZNεP decreases methylation of multiple other histone residues, perhaps as a result of the ability of SAH to compete with the AdoMet cofactor (25). Hence, more specific inhibitors of EZH2 are required to address various lesions.
in cancer. The recently introduced GSK126 molecule is the first-in-class inhibitor of EZH2, acting as a SAM competitor and affecting specifically the HMT activity of EZH2 (26). DLBCL cell lines expressing mutant EZH2 are highly sensitive to GSK126, suggesting that direct inhibition of EZH2 activity presents a promising avenue for treatment in the clinic.

**NSD Proteins**

The NSD (nuclear receptor SET domain-containing) family of histone methyltransferases, methylate H3K36, is a modification implicated in transcription, DNA repair, and alternative splicing. Actively transcribed genes are enriched for H3K36me3, where the mark precedes adventitious initiation of transcription from within the gene body (5, 27). The three members of this protein family (NSD1, 2, and 3) contain PHD and PWWP domains, important for chromatin recognition, as well as the SET domain. NSD1 (KMT3B) can methylate nonhistone substrates such as NF-kB, a function likely preserved in NSD2 (WHSC1/MMSET) and NSD3 (WHSC1L1) (28), suggesting that chromatin-centric studies may be insufficient to decipher how HMTs drive disease.

NSD1 is mutated in Sotos syndrome, a disorder characterized by developmental overgrowth and cognitive disabilities (29). In a small number of cytogenetically normal cases of AML, chromosomal translocation fuses the N-terminus of NUP98 to the C-terminal portion of NSD1, including the SET domain (30). NUP98-NSD1 protein can immortalize progenitor bone marrow cells, activate Hox gene expression, and induce AML in mice (31) in a manner dependent on H3K36 methylation. NSD3 is also translocated with NUP98 locus in rare cases of AML (32) and increased NSD3 expression occurs in approximately 15% of breast cancers (33). Furthermore, NSD3 readily transformed breast cell lines and cells overexpressing NSD3 cease proliferation on its depletion (34). Deletions of the _WHSC1_ gene lead to Wolf-Hirschhorn syndrome (WHS), which is characterized by cognitive and developmental defects (35). _WHSC1_ was linked to malignancy as a result of its rearrangement with the immunoglobulin locus and overexpression in approximately 20% of cases of multiple myeloma. Knockdown of _WHSC1_ in myeloma cells slows cell growth, alters cellular adhesion, and induces apoptosis (36). _WHSC1_ levels are also frequently elevated in advanced-stage solid tumors (37). _WHSC1_ was recently shown to be a critical factor for repair of double-stranded DNA damage, but how this function correlates with its oncogenic activity is uncertain (38).

Overexpression of _WHSC1_ in myeloma leads to a genome-wide increase of H3K36me2 and concomitant decrease of H3K27me3 (Fig. 1B) (36). The NUP98-NSD1 fusion has a similar but more localized effect on chromatin of _HOX_ genes, activating their expression (31). These data are consistent with previous reports indicating that H3K36 methylation inhibits PRC2-mediated H3K27 methylation (39). Which genes and pathways are deregulated by this epigenetic switch in myeloma remains to be fully defined. Nevertheless, this is another example of altered H3K27 methylation as a possible driver of tumorigenesis, suggesting that inhibitors of NSD proteins may be useful for specific tumors.

**H3K9 Methyltransferases**

The first enzymatically active SET domain-containing HMT described was SUV39H1 (KMT1), belonging to the family of H3K9-specific methyltransferases (40). Although H3K9 methylation is generally associated with transcriptional repression related to heterochromatin formation and DNA methylation, there is also evidence linking K9 methylation to transcriptionally active loci (41). H3K9 HMTs have been found upregulated in various human tumors. Consistent with this finding, downregulation of G9a (KMT1C), another H3K9-specific HMT, suppresses tumor cell growth and invasion in mice (42). Two small molecules, Chaetocin and BIX01294, specifically inhibit H3K9 HMTs through AdoMet and histone tail competitive inhibition, respectively (43–45). Given the role of H3K9 methylation in proviral silencing, it is unclear whether the drugs would have undesirable effects and what their effect may be in normal cells.

**PROTEIN ARGinine METHyLTRANSFERASES**

There have been nine different arginine methyltransferases identified to date (PRMT1–9) and methylation of arginines is associated with both positive and negative regulation of transcription. Consequently, recent evidence points to the role of arginine methylation in oncosogenesis, including hematologic and solid tumors (46). Similar to lysine methyltransferases, RMTs can modify nonhistone targets, including p53, and affecting its target gene specificity (47). Moreover, RMTs’ function can be affected by oncogenic pathways. For example, constitutively active JAK2<sup>617H</sup> mutant phosphorylates PRMT5 function, impairing its methyltransferase activity and promoting myeloproliferation (48). Although initial arginine methyltransferase inhibitors (AMI) have been tested _in vitro_ for their efficacy and selectivity, data regarding their usefulness in cellular and animal models have been sparse. A better understanding of the roles RMTs may play in disease will enhance the opportunity for testing these and other newer classes of AMIs.

**HISTONE DEMETHyLASES**

Histone methylation is counteracted by histone demethylases (HDM), including LSD1 (KDM1), a flavin adenine dinucleotide-dependent amine oxidase, and Jumonji C (JmJC) lysine and arginine demethylases, which use α-ketoglutarate and Fe<sup>2+</sup> ions as cofactors. Although LSD1 can only remove methyl groups from mono- or dimethylated H3K4 or H3K9, JmJC enzymes can catalyze removal of trimethyl marks. Like HMTs, HDMs function can be altered in cancer.

**UTX (KDM6A)**

H3K27, the site of frequent epigenetic anomalies, is demethylated by UTX/UTY and JMJD3, all belonging to the JmJC subgroup. _UTX_, found on a pseudoautosomal region of Xp11.2 and _UTY_, encoded on the Y chromosome, shared a high degree of homology. JMJD3 (KDM6B) is a related protein but is missing a tetratrico peptide repeat interaction domain found in UTX/UTY. The roles of UTX/UTY and JMJD3 in development are context dependent, tissue specific, and nonoverlapping (49, 50).
MJJD3 displays occasional mutation in cancer of uncertain significance (51). By contrast, somatic loss-of-function mutations of UTX are found in multiple myeloma (10%), esophageal squamous cell (8%), renal carcinomas (1%), and occasionally in breast, AML, glioblastoma, colorectal, and bladder cancer (52). UTX mutant tumors tend to suffer deletion of UTY, suggesting a drive toward complete loss of function of these proteins. Genes affected by UTX mutation displayed increased levels of H3K27me3, but global levels of H3K27 methylation are not altered, suggesting that UTX is primarily involved in chromatin demethylation at specific regulatory sequences (Fig. 1B). Indeed, UTX forms a complex with MLL2, an H3K4 HMT (53), suggesting a mechanism in which UTX removes repressive H3K27 methylation while MLL2 places activating methylation. Loss of UTX function may lead to inappropriate gene silencing by Polycomb complexes and as a result, such tumors might also be amenable to therapy with EZH2 inhibitors. By contrast, tumors with loss of EZH2 function might be amenable to UTX/MJD3 inhibitors with an aim of restoring levels of H3K27me3.

**IDH1/2-METABOLIC MUTATIONS AFFECTING EPIGENETIC REGULATION**

Genome sequencing of glioblastoma and AML identified recurrent, heterozygous missense mutations in IDH1 and IDH2, encoding isocitrate dehydrogenases that catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the cytoplasm and mitochondria, respectively (54, 55). IDH1/2 lesions occur in approximately 70% of low-grade brain tumors and 20% of AML and can be found in other myeloid neoplasms and chondrosarcoma (56, 57). Instead of oxidizing isocitrate to α-KG, mutant IDH reduces α-KG to 2-hydroxyglutarate (2-HG) (58). As a result, α-KG levels drop and 2-HG levels, normally barely detectable, are dramatically elevated. This has profound effects on the epigenetic state of the cell.

2-HG is a competitive inhibitor of α-KG–dependent enzymes. In leukemia, IDH mutations disrupt the function of TET2, which encodes an enzyme that converts 5-methylcytosine to 5-hydroxymethylcytosine, a step on the way to DNA demethylation (59). In AML, mutations in IDH1/2 and TET2 are mutually exclusive, suggesting that they have a common function. Indeed, increase in 2-HG inactivates TET proteins and leads to DNA hypermethylation. The 2-HG/α-KG imbalances also can inhibit prolyl hydroxylases, which downregulate hypoxia-inducible factor-1α (HIF-1α), a transcription factor involved in response to hypoxia and implicated in malignancy (60). However, recent data also suggest that (R)- but not (S)-enantiomer of 2-HG can enhance activity of prolyl hydroxylase EGLN, leading to diminished HIF-1α levels (61). Furthermore, 2-HG also inhibits JmJ C histone demethylases (60) and IDH1 mutations can induce hypermethylation of histone H3 lysine residues 4, 9, 27, and 79 (Fig. 1B). In addition, α-KG–dependent arginine demethylases, like JMJD6, are also likely to be affected by elevated 2-HG (62). Why IDH1/2 mutations are found in such a limited set of tumors remains uncertain but might be related to the dependence of brain, blood, gallbladder, and cartilage on specific sets of α-KG–dependent epigenetic regulators to control cell growth. Lastly, reduction of α-KG to 2-HG is predicted to deplete NADPH, a stoichiometric cofactor for sirtuins, histone deacetylases that affect chromatin and nonhistone proteins. Drugs targeting mutant IDH proteins are in development. Enforced expression of mutant IDH1 or IDH2 in erythroleukemia cells stimulated growth factor-independent myeloid growth and downregulation of GATA1, an effect reversed by an agent that inhibits the mutant IDH enzyme (63). Further identification of the key enzymes inhibited by 2-HG and biomarkers of on-target effects will be required to interpret the action of such drugs.

**BLOCKADE OF EPIGENETIC READERS**

The epigenetic enzymes are an obvious choice for targeted therapy, but equivalently important are modules that interpret the epigenetic code. Directly or through recruitment of other transcriptional regulators, these proteins play essential roles in the control of gene expression.

**BRD4**

Bromodomain-containing proteins affect gene regulation through their ability to bind acetylated histone lysine residues. BRD4, a BET (Bromodomain and Extra-Terminal) protein, stimulates transcriptional elongation by recruitment of the P-TEFb complex, which phosphorylates and increases the processivity of RNA polymerase II, leading to expression of growth-promoting genes (64). In rare, t(15;19)-associated lethal midline carcinoma, the resulting BRD4-NUT fusion contains two BRD4 bromodomains that aberrantly bind and sequester acetylated histones, leading to a global hypoacetylation of chromatin, a block of differentiation, and stimulation of proliferation (65). Treatment of BRD4-NUT+–positive cell lines with HDAC inhibitors is a true form of epigenetic differentiation therapy that leads to chromatin acetylation, the induction of sheets of differentiated, squamous epithelium, and terminal cell division (66). An alternative way to inhibit BRD4 is to block its ability to bind to acetylated lysine (Fig. 2). A synthetic molecule, I-BET, binds to the acetylated lysine-binding pocket of BET proteins, preventing their recruitment to target genes (67). This limits the recruitment of P-TEFb and Pol II and decreases histone acetylation and transcription. Filipakopoulos and colleagues (68) identified JQ1, a molecule that blocks BET/acyt histone interaction, with greatest specificity for the BRD3 and BRD4. JQ1 displaces BRD4 from chromatin and induces differentiation and growth arrest of a midline carcinoma cell line in vitro and in mouse xenografts, phenocopying changes seen by siRNA-induced knockdown of the BRD4-NUT (Fig. 2A).

Bromodomain inhibitors may have broader uses as well. JQ1 was applied to a panel of multiple myeloma cells and led to decreased cell growth (69, 70). Gene expression profiling showed that this was accompanied by a decline of c-MYC target genes, explained by a dramatic decrease in c-MYC transcription. Notably, JQ1 inhibited growth of cell lines resistant to dexamethasone and melphalan, two standard agents for myeloma. Although many chemotherapeutic drugs become ineffective when cells are cultured on stromal cells, growth inhibition by JQ1 was unaffected. Furthermore, JQ1 decreased disease burden and extended survival in a c-MYC-driven mouse model of myeloma. The use of BRD4 blockade was further extended to leukemia, because a short-hairpin RNA
screen in a mouse AML model identified Brd4 as a critical gene for leukemia cell survival (71). Accordingly, JQ1 blocked the ability of Brd4 to bind to c-myc regulatory elements of these cells and inhibited their growth.

These encouraging studies should motivate the targeting of other histone reading modules such as PHD fingers, chromodomains, Tudor domains, and PWWP domains. The crystal structures of many of these domains bound to their cognate histone residues are solved and may facilitate the design of such molecules. However, because many of these domains are widely distributed in many epigenetic regulators and may show a high degree of structural and functional similarity, the specificity of histone-binding domain inhibitors may be crucial for their clinical use.

PROTEIN INTERACTION BLOCKADE

Although epigenetic enzymes and chromatin-binding domains represent more traditional drug targets, recent evidence indicated that indeed transcription factors and their interplay with cofactors could be targeted.

BCL6

BCL6, a transcription factor critical for the development of germinal center B cells, represses the activity of p53 in a developmental stage-specific manner to prevent apoptosis in response to DNA damage generated during somatic mutagenesis used to produce antibody diversity (72). Aberrant overexpression of BCL6 in diffuse large B-cell-lymphoma stimulates malignancy by continuous inhibition of such pathways. BCL6 contains a BTB repression domain that is unique in its ability to tightly bind to the corepressor NCOR and related SMRT protein through a specific groove (73). A BCL6 peptide inhibitor, based on the portion of SMRT bound to BCL6, blocks BCL6-mediated repression, activates BCL6 target genes, and selectively inhibits growth of DLBCL cell lines overexpressing BCL6 [Fig. 2B (74)]. The use of this approach may extend beyond lymphoma. BCL6 is upregulated in chronic myelogenous leukemia in response to the tyrosine kinase inhibitor imatinib, possibly representing a general response to cellular stress. Treatment of mice with anti-BCL6 peptide and imatinib eradicated BCR-ABL–positive leukemia cells, whereas imatinib alone did not (75).

BCL6 represses the histone acetyl transferase p300, suggesting that the combination of BCL6 blockade and histone deacetylase inhibitors could be a useful combination for some forms of lymphoma (76).

MLL–MENIN INHIBITORS

Recruitment of the WT MLL and MLL fusion proteins to target sequences require direct interaction with menin, a tumor-suppressor gene that plays a role in transcriptional activation (77). Menin is required for transcription of MLL target genes and for induction of leukemia by MLL fusion proteins. Recently, Grembecka and colleagues (78) identified a small molecule (MI-2) that specifically blocks MLL–menin interaction (Fig. 1A). Consequently, MI-2 induced growth arrest and differentiation and blocked colony formation of mouse progenitor cells transduced with MLL-AF9 or MLL-ENL. Treatment of human leukemia prevented recruitment of MLL fusion proteins to their gene targets and suppressed cell growth, findings that phenocopy the effects of menin downregulation. However, because WT MLL also requires menin, it remains to be determined whether these agents will adversely affect MLL-dependent normal hematopoiesis.

CONCLUSIONS

The past decade led to the identification and characterization of new enzymes and protein–protein interactions required for the epigenetic regulation of gene expression,
a subset of which are dysregulated in cancer. Broadly acting therapies such as HDAC inhibitors have now been succeeded by molecules that target specific epigenetic regulators and specific transcription factors. Novel inhibitors affecting H3K27 are clearly needed, because deregulation of this modification seems to be a unifying component in a number of different malignancies. Inhibitors of H3K36 methylation, agents that block aberrant activity of mutant IDH, and molecules that interfere with the "reading" of the histone code all represent agents that should be prioritized for development.

Disclosure of Potential Conflicts of Interest
J.D. Licht received a commercial research grant from Epizyme; and is a consultant/ advisory board member of GlaxoSmithKline. No potential conflicts of interest were disclosed by the other author.

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