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Targeting epigenetic regulators for cancer therapy

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Human gene expression patterns are controlled and coordinated by the activity of a diverse array of epigenetic regulators, including histone methyltransferases, acetyltransferases, and chromatin remodelers. Deregulation of these epigenetic pathways can lead to genome-wide changes in gene expression, with serious disease consequences. In recent years, research has suggested that cross talk between genomic (i.e., for example, mutations, translocations) and epigenomic factors may drive the etiology of both hematologic malignancies and solid tumors. Current work in translational research seeks to identify epigenetic regulators whose aberrant activity contributes to oncogenesis, including the histone methyltransferases DOT1L and EZH2 and the bromodomain-containing BET family, and to develop drugs that inhibit the aberrant activity of these regulators. Preclinical and clinical studies using small-molecule inhibitors of epigenetic regulators have underscored their value for therapeutic intervention, and these inhibitors can also be used to drive further studies into dissecting the functions of epigenetic factors in normal and cancer cells.

Keywords: epigenetic regulators; cancer therapy; drug discovery; DOT1L; EZH; MLL

Introduction

Recognition of the importance of epigenetics in regulating cell physiology in normal and disease states has spawned intense research activity in academia and within biotechnology and pharmaceutical companies. Although a spectrum of outcomes for the work is envisaged, there is a unifying desire to develop a deeper understanding of the role and function of chromatin-binding proteins and the associated transcriptional machinery. Ultimately, such knowledge is anticipated to help uncover important disease-associated epigenetic mechanisms or pathways and to spur the development of novel therapeutics.

Undoubtedly, the strongest case for epigenetic misregulation currently exists in oncology. The discovery of somatic mutations, chromosomal translocations, and other events in chromatin-associated proteins has highlighted the critical contributions of altered chromatin function in various heme malignancies.[1] Epigenetic alterations have been observed early in carcinogenesis and may develop with a greater frequency than changes in DNA sequence, leading to changes in gene expression and signaling pathways.[2–4] Epigenetic alterations in cancers are often observed in tumor-suppressor genes, and many of the epigenetic regulators responsible for silencing these genes are deregulated in cancer.[5] Cancer genome analyses have identified recurrent mutations of histone- and DNA-modifying enzymes and nucleosome-remodeling complexes. In this context, there is an increasing acceptance of integrated cross talk between key genomic drivers and emerging epigenomic factors in disease etiology, at all stages of cancer development. Indeed, evidence supporting the extension of this idea to solid tumors continues to accumulate.[6] The dynamic and reversible nature of epigenetic modifications makes epigenetic enzymes appealing drug targets for cancer therapy.

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First-generation epigenetic inhibitors, including DNA methyltransferase inhibitors and histone deacetylase inhibitors, have already been approved for cancer therapy. Current drug development efforts are focused on investigating more selective inhibitors that target a single epigenetic enzyme or a small subset of enzymes deregulated in cancers.

The unique one-day symposium "Targeting Epigenetic Regulators for Cancer Therapy," held on May 24, 2013 at the New York Academy of Sciences, brought together leading investigators involved in elucidating fundamental aspects of chromatin biology and identifying the enzymes and/or reader proteins involved in aberrant interpretation of the histone code, drug discovery and development scientists, and clinicians charged with translating preclinical hypotheses for patient benefit.

New advances in deciphering the epigenetic code

Recent progress suggests that the "on" or "off" states of chromatin are not simply determined by a single histone or epigenetic mark. In fact, chromatin modifications often exist in pairs or as a pattern to mediate or disrupt certain downstream molecular recognition events, thereby contributing to the establishment and maintenance of particular cellular traits.

In the morning session, Haitao Li (Tsinghua University) highlighted how chromatin regulators make use of paired or integrated reader modules to translate particular epigenetic signatures into unique functional outcomes in health and disease. Histone posttranslational modifications (PTMs) and DNA methylation are considered to constitute a layer of epigenetic codes that help to organize the genetic information at the chromatin level and that play an important role in gene expression, cell differentiation, and development.[7] Histones can undergo diverse modifications. Figure 1A summarizes the major chemical types of known histone PTMs. In addition to the classical histone PTM types, such as methylation (me), acetylation (ac), and phosphorylation (ph), recently identified histone modifications include new forms of histone acylation (crotonylation, formylation, propionylation, and butylation), glycosylation, and lipidation. To date, about 25 distinct chemical types of histone PTMs have been identified, and if taking the site information into account, the number of distinct histone PTMs can easily be expanded to more than 250 among all histones. Each particular histone PTM functions like a marker to index the genome, and is usually recognized by particular histone binding effector or reader modules to bring about specific functional outcomes.[8] Interestingly, the reader modules that usually recognize histone markers in a type- and site-specific manner are often linked in tandem in one protein or coexist within a complex, which strongly suggests a combinatorial mechanism of histone modification signature readout.[9]

Li reported on the molecular basis for histone PTM pattern decoding by paired reader modules such as Tudor, PHD, bromo-, and ADD domains. Figure 1B showcases two examples of combinatorial readout. One is trimethylation of the *trans*-tail histone H3K4 (H3K4me3) and acetylation of H4K16 (H4K16ac), read out by paired PHD-linker-bromodomains of BPTF at the single nucleosome level. BPTF is the largest subunit of the nucleosome remodeling factor (NURF) complex, which catalyzes nucleosome sliding on DNA to facilitate transcription. *In vivo* functional studies established that the multivalent recognition of H3K4me3–H4K16ac by BPTF is required for controlling the expression of *HOXA9*, a gene that is critical for embryonic development and whose dysregulation is often linked to leukemia. The other case is the single-tail histone lysine methylation pattern read out by the ADD domain of ATRX—an SNF2 family ATPase/helicase remodeler associated with heterochromatin.[10] Mutations of the *ATRX* gene are the causative factors of X-linked α-thalassemia/mental retardation syndrome. Recent whole-exome sequencing analyses revealed a connection between *ATRX* somatic mutations and pancreatic neuroendocrine tumors and pediatric glioblastoma. The ADD domain is a hybrid of a GATA-like zinc finger and a PHD finger. Complex structure analysis established that ADD readout of histone PTMs depends on an unmodified state of H3K4 (H3K4me0) and a trimethylated state of H3K9 (H3K9me3). Notably, Li continued, recognition of H3K9me3 is realized by a composite pocket at the interface of the GATA-like and PHD fingers, calling attention to the strategy of module integration for gain of new reader activity. Additionally, functional studies revealed that the H3K4me0–K9me3 sensor activity of ADD is critical for ATRX targeting of heterochromatin. As a footnote, nearly half of the patient mutations are clustered to the ADD

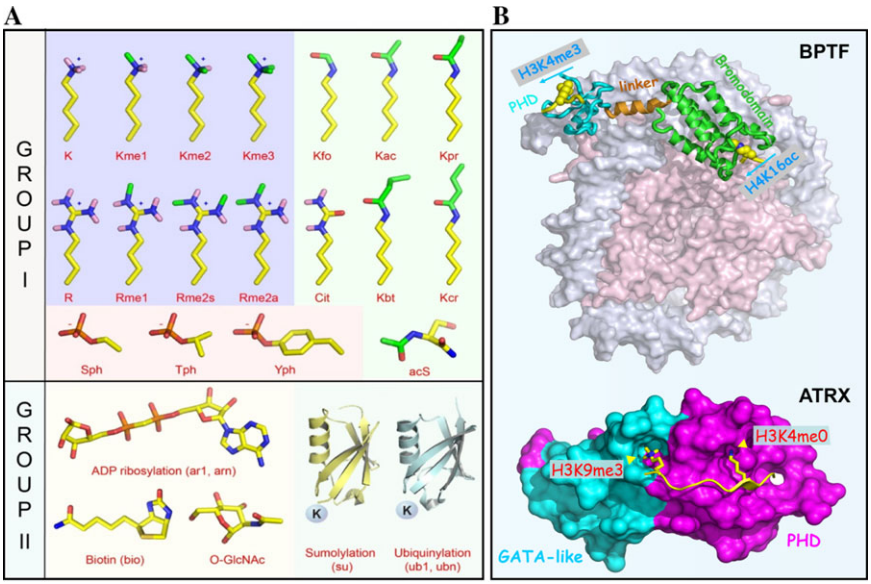

Figure 1. Histone posttranslational modifications (PTMs) and their combinatorial readout. (A) Major chemical types of PTMs identified in histones. Group I, small chemical moiety modifications; Group II, large chemical group modifications. Color coding in stick mode: hydrogen, pink; methyl group, green; oxygen, red; nitrogen, blue; carbon, yellow; phosphorus, orange. SUMO and ubiquitin are in ribbon representation. (B) Combinatorial readout of histone PTM patterns. (Upper) Recognition of a *trans*-tail H3K4 trimethylation (H3K4me3) and H4K16 acetylation (H4K16ac) pattern by BPTF tandem PHD inker bromodomains on a single nucleosome. The nucleosome is in surface representation with core histone octamer colored in pink and DNA colored in gray. (Lower) Recognition of an unmodified H3K4 (H3K4me0) and trimethylated H3K9 (H3K9me3) signature by ATRX ADD domain. Note that ADD is a hybrid of a GATA-like finger (cyan) and a PHD finger (magenta).

domain, indicating the importance of ADD in histone methylation pattern decoding.

Current epigenetic approaches for cancer therapeutics

Leukemias harboring rearrangements of the myeloid/lymphoid leukemia (*MLL*) gene carry a poor prognosis. Over the past 6 years, it has become increasingly clear that fusions of *MLL* induce widespread epigenetic deregulation that may mediate much of their transforming activity.[11,12] The histone methyltransferase DOT1L, which methylates histone 3 on lysine 79 (H3K79), has received particular attention. Genome-wide H3K79 methylation profiles in *MLL*-rearranged leukemias are abnormal, and can serve to distinguish *MLL*-rearranged leukemia from other types of leukemias.[12–15] Loss of H3K79 methylation affects expression of *MLL* target loci and is detrimental to the leukemogenic activity of *MLL*-rearranged cells, suggesting that a DOT1L-dependent, aberrant epigenetic program drives transformation in these leukemias. Small-molecule DOT1L inhibitors have been developed that selectively inhibit proliferation of *MLL*-rearranged leukemia cells.[12,16] These molecules are now in clinical trials for patients with relapsed refractory leukemia and will be discussed below in greater detail.

Scott A. Armstrong (Memorial Sloan-Kettering Cancer Center) presented on recent progress made in his laboratory on DOT1L and the polycomb repressive complex 2 (PRC2). Conditional inactivation of DOT1L in mouse models of *MLL*-rearranged leukemia leads to a decrease in *MLL*-fusion target gene expression, leukemia cell differentiation, and loss of leukemogenic activity. He showed that inactivation of other members of the Dot1L complex, such as Af10, lead to a decrease in H3K79 methylation and *MLL*-fusion target gene expression, thus suggesting other potential therapeutic approaches. Armstrong also presented on the use of conditional alleles for the PRC2 components enhancer of zeste 2 (*Ezh2*) and embryonic ectoderm development (*Eed*) to characterize the role of PRC2 function in leukemia development and progression.[13] PRC2 has been implicated

in self-renewal and cancer progression, and its components are overexpressed in many cancers, but its role in cancer development and progression remains unclear. Compared to wild-type leukemia, *Ezh2*$^{-/-}$ *MLL/AF9*-mediated acute myeloid leukemia (AML) showed decreased organ infiltration and failed to accelerate upon secondary transplantation. These data show that histone-modifying enzymes play critical roles in leukemia and may be relevant therapeutic targets in these diseases.[17]

Robert A. Copeland (Epizyme, Inc, Cambridge, MA) discussed the protein methyltransferases (PMTs) as drug targets for personalized cancer therapeutics.[18] He began by presenting an overview of this enzyme class, which in humans comprises 96 putative enzymes that divide into two distinct families: the protein lysine methyltransferases (PKMTs) and the protein arginine methyltransferases (PRMTs).[18] Copeland went on to describe a variety of mechanisms by which genetic alterations can confer a unique dependency of cancer cells on the enzymatic activity of specific PMTs. These mechanisms include direct and indirect chromosomal translocations, amplifications, change-of-function mutations within the PMT, loss-of-function mutations within a corresponding protein demethylase, ectopic gene localization of PMTs, and synthetic lethal relationships. Copeland then presented studies on two PMTs, DOT1L,[14,16] and EZH2,[15,19] that exemplify the range of genetic alterations seen associated with PMTs in human cancers.

As introduced above by Armstrong, Copeland described how DOT1L enzymatic activity is thought to be a driver of leukemogenesis in *MLL*-rearranged leukemia. This hypothesis has been tested by the discovery and optimization of a potent, selective DOT1L inhibitor, EPZ-5676 (Table 1), which selectively kills cells containing the *MLL* chromosomal translocation, while showing little effect on leukemia cells lacking this translocation. In a rat xenograft model of *MLL*-rearranged leukemia, EPZ-5676 showed significant tumor growth inhibition, with complete eradication of tumors at the higher doses tested. At the higher dose, animals treated for 21 days by continuous intravenous administration of EPZ-5676 remained tumor free until the end of the study period, 53 days in total (i.e., 32 days past the end of the treatment period). EPZ-5676 has now advanced to phase 1 human clinical trials.[14]

EZH1 or EZH2 is the catalytic subunit of the multiprotein complex PRC2, which is responsible for the methylation of histone H3 on lysine 27 (H3K27).[17] H3K27 can be mono-, di-, or trimethylated, and PRC2 is responsible for all three of these enzymatic methylation reactions. EZH2 has been implicated in a number of hematologic and solid human cancers.[20] Most recently, point mutations within the catalytic domain of EZH2 have been found to occur in subsets of patients with non-Hodgkin lymphoma (NHL). These mutations were at first thought to be loss-of-function mutations, but were subsequently shown to change the substrate specificity of EZH2 and to work in concert with the wild-type enzyme to affect a hyperproliferative phenotype in mutant-bearing NHL patients.[15,18,19] Several potent, selective inhibitors of EZH2 have been reported in the literature. For example, EPZ-6438 (also known as E7438; Table 1) is an orally bioavailable, nanomolar, *S*-adenosylmethionine competitive inhibitor of EZH2 that displays significant selectivity with respect to inhibition of other PMTs.[15] This compound selectively kills NHL cells bearing mutations within *EZH2*, while having minimal effect on the proliferation of *EZH2* wild-type NHL cells. Oral administration of EPZ-6438 twice-daily for 28 days to mice bearing human *EZH2*-mutant NHL tumors resulted in dose-dependent tumor growth inhibition, with complete eradication of the tumors at the higher doses tested. As was the case with the DOT1L inhibitor (see above), no regrowth of tumors was observed in the higher dose group animals for up to 32 days after ending the dosing period, which was the termination point for the study. EPZ-6438 is expected to enter human phase 1 clinical testing soon. Copeland went on to describe the efficacy of EPZ-6438 in treating malignant rhabdoid tumor cells in culture and in mouse xenograft models.[15] The compound was very effective in preclinical models of this pediatric solid tumor, suggesting that inhibition of EZH2 may be an effective mechanism of treatment for multiple human cancer indications.

Robert Sims (Constellation Pharmaceuticals) expanded the discussion on current epigenetic cancer therapeutics by introducing the BET family of chromatin adaptors. The bromodomain and extra terminal (BET) domain proteins contain tandem bromodomains that recognize specific acetylated lysine residues in the N-terminal tails of histone proteins. Consequently, members of the BET

Table 1. Characteristics of the DOT1L inhibitor EPZ-5676 and the EZH2 inhibitor EPZ-6438

Parameter	EPZ-5676	EPZ-6438
Target enzyme	DOT1L	EZH2
Enzyme K_{i-} (nM)	<0.08	2.5
PMT selectivity	>37,000-fold	>4500-fold
Inhibition of intracellular methylation IC_{50} (nM)	2.7 (H3K79me2)	260 (H3K27me3)
Inhibition of cell proliferation IC_{50} (nM)	3.5 (MV4-11 cells)	280 (WSU-DLCL2 cells)

family, including BRD2, BRD3, BRD4, and BRDT, have been shown to selectively regulate transcription of key cancer gene expression. Recently, Sims and others have described the rapid and potent abrogation of *MYC* gene transcription by small-molecule inhibitors of the BET family bromodomains.[21,22] Treatment of MYC-dependent cancer cells with BET inhibitors results in growth arrest and apoptosis in cell culture and antitumor activity in xenograft animal models of multiple myeloma, lymphoma, and acute leukemia.[22] Sims also discussed the characterization of the molecular impact of BET bromodomain inhibition, specifically in the context of global chromatin reorganization and transcriptional control. Upon inhibitor treatment, he described a global alteration in BET and MYC chromatin localization, histone modifications, and RNA polymerase II distribution. Despite this, a remarkably small subset of genes is observed to be direct BET transcriptional targets. Specifically, transcriptional profiling studies revealed that only 2% of BRD2- or BRD4-bound genes, as identified by ChIP-Seq, are downregulated by twofold or more in gene expression–profiling studies. Interestingly, many of the genes targeted by BET inhibition were found to be transcription factors. Additionally, Sims discussed Constellation's drug discovery platform, which utilizes biochemical screening, structural biology, medicinal chemistry, and *in vivo* pharmacology to develop a series of BET bromodomain inhibitors that are highly potent, selective, and optimized for clinical development. From these efforts, CPI-BETi has been identified as a potent and selective small-molecule inhibitor. Treatment of an AML xenograft model with CPI-BETi at 1.5 mpk twice-daily subcutaneously resulted in tumor regression with no significant body weight loss or adverse events. Constellation has initiated a phase 1 clinical trial of their novel BET protein inhibitor CPI-0610 in patients with previously treated and progressive lymphomas. Future clinical studies of CPI-0610 are planned in patients with multiple myeloma, acute leukemia, or myelodysplastic syndrome.

Future clinical outlook for epigenetic therapy

Through ever-building genome-wide mapping studies, knowledge of how normal genomes are constructed is dramatically informing our view of epigenetic abnormalities in cancer, and vice versa. From an era that began with recognizing cancer-specific abnormalities in DNA methylation, both losses and gains, we now understand that these must not only be linked to defining key-associated chromatin changes, but also viewed in the context that all genomic regions are not equal for susceptibility to these alterations.[23] A critical example is the revelation that both the losses and gains of DNA methylation in cancer can be biased to distinct genomic regions with nuclear lamin–associated, late-replicating DNA that is enriched for low-transcription developmental genes with promoter region bivalent chromatin.[24] Such chromatin, in embryonic and adult stem cells, is essential for maintenance of the stem cell state and appears vulnerable for evolving epigenetic abnormalities during tumor progression. This vulnerability may heavily involve stresses, such as increased ROS, which acutely shifts a complex of proteins, involving DNA methyltransferases and polycomb proteins, into CpG islands. Retention of such proteins may start the process of abnormal DNA methylation. These scenarios have tremendous implications for whether epigenetic abnormalities help to keep key cell subpopulations in cancers from properly leaving the self-renewal state and/or blocking their commitment to cell lineages and differentiation. If this is the case, the biology described above has exciting translational implications for possible epigenetic and/or differentiation therapy for cancer and for molecular signatures that can guide such treatments.[25] Already, exciting examples of the

efficacy of such approaches have emerged and these will undoubtedly increase dramatically in the future. Among other examples discussed at the conference was the potential for epigenetic therapy to change the management of advanced non-small cell lung cancer (NSCLC), including sensitization of NSCLC patients to subsequent chemotherapy and a new form of immunotherapy, including the potential for low-dose use of 5-aza-cytidine to blunt the above-mentioned type of stem cell activity in some cancers.

Conclusion

In conclusion, this symposium brought together basic scientists and clinicians, from academic researchers to drug hunters from around the globe. The meeting began with presentations on epigenetic research steeped in basic biology and ended with talks on the current state of epigenetic therapy in the clinical setting.

Revelations from next-generation sequencing studies have made a strong case for targeting epigenetic regulators as cancer drug targets. Sequencing of entire tumor genomes have revealed mutations in chromatin-modifying enzymes in nearly all tumors profiled. Elegant studies on two epigenetic regulators, EZH2 and BRD4, presented by Copeland and Sims, respectively, have confirmed the proliferative dependency of cancer cells on these mutations. Even in the absence of genetic alterations, as in the case of DOT1L, the association of epigenetic regulators with larger deregulated chromatin complexes identifies them as excellent drug targets. Armstrong presented evidence of progress on DOT1L inhibitors currently in clinical trials as a promising therapy in leukemias harboring *MLL* gene rearrangements. Preclinical and clinical studies such as these have validated the functional relevance of mutations in epigenetic targets, further underscoring their value for therapeutic intervention.

The deeper scientific understanding of the normal physiological functions of epigenetic writers, readers, and erasers draws attention to the desired selectivity profiles or even potential liabilities associated with epigenetic targets. The efforts to develop high resolution structure of epigenetic regulators will lay a good foundation for rational drug design.[26] The discovery of small molecules to intervene with the activity of epigenetic regulators, on the other hand, provides chemical tools to further dissect the functions of these proteins through genome-wide studies, such as ChIP-seq analysis, as discussed by Shirley Liu (Dana Farber Cancer Center).[27] As a result, valuable information has been generated for possible biomarkers of disease response and subsequent clinical-trial design and patient-stratification strategies.

This symposium also highlighted challenges and opportunities ahead. Alexander Tarakhovsky (The Rockefeller University) and Liu presented unpublished work on a role for EZH2 in cell-context–dependent signaling pathways beyond its more established role as a histone methyltransferase.[27] Clearly, there is much to be learned about the role of epigenetic targets beyond chromatin regulation. Finally, Stephen B. Baylin (The Johns Hopkins School of Medicine) presented evidence of new opportunities for hypomethylating agents currently approved for treatment in myelodysplastic syndromes. On the basis of preclinical studies from his group, there is strong evidence to suggest that the optimization of dosing and scheduling of these agents will result in better efficacy and tolerability in solid tumors. Multiple clinical trials to address this possibility are ongoing.

In summary, this symposium demonstrated the positive synergy between academic and industry research in the field of epigenetics and its implications for translational research. As highlighted throughout the day's presentations, the parallel advancements in our scientific understanding of chromatin biology and the discovery of small molecular drug candidates targeting epigenetic regulators have unlocked a new and exciting area of cancer drug discovery.

Conflicts of interest

R.A.C. is an employee and stockholder of Epizyme, Incorporated. S.W. and L.S. are employees of Bristol-Myers Squibb, and R.S. is an employee of Constellation Pharmaceuticals.

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