# Exploiting the Epigenome to Control Cancer-Promoting Gene-Expression Programs

Gerard L. Brien,[1,2] Daria G. Valerio,[1,2] and Scott A. Armstrong[1,2,3,*]
[1]The Center for Epigenetics Research
[2]Cancer Biology and Genetics Program
[3]Department of Pediatrics
Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
*Correspondence: armstros@mskcc.org
http://dx.doi.org/10.1016/j.ccell.2016.03.007

**The epigenome is a key determinant of transcriptional output. Perturbations within the epigenome are thought to be a key feature of many, perhaps all cancers, and it is now clear that epigenetic changes are instrumental in cancer development. The inherent reversibility of these changes makes them attractive targets for therapeutic manipulation, and a number of small molecules targeting chromatin-based mechanisms are currently in clinical trials. In this perspective we discuss how understanding the cancer epigenome is providing insights into disease pathogenesis and informing drug development. We also highlight additional opportunities to further unlock the therapeutic potential within the cancer epigenome.**

## Introduction

Epigenetics refers to heritable traits that are not attributable to changes in DNA sequence. In more specific terms, it can be used to describe how chromatin-associated proteins and reversible chemical modifications of DNA and histone proteins maintain transcriptional programs by regulating chromatin structure (Strahl and Allis, 2000). Since all cells in a multicellular organism contain essentially the same DNA, the development of specialized cell types requires a tightly regulated process that leads to the expression of genes critical for a specific cell type and repression of genes required for alternative cell fates. One important process by which cells regulate cell-type-specific gene expression is the packaging of DNA into chromatin in a fashion that modulates transcriptional output in a given cell type. Therefore, epigenetic regulatory mechanisms are instrumental in dictating cell identities and have been implicated in fundamental processes such as development, stem cell self-renewal, differentiation, genome integrity, and proliferation (Tessarz and Kouzarides, 2014). Epigenetic gene regulation is primarily achieved through the collaboration of multiple regulatory pathways involving sequence-specific DNA-binding transcription factors, long non-coding RNAs (lncRNAs), ATP-dependent nucleosome remodeling, DNA methylation, introduction of histone variants, and post-translational modification (PTM) of histone proteins. Histone proteins can be modified at specific amino acid residues by diverse chemical moieties including methylation, acetylation, phosphorylation, ubiquitination, and SUMOylation (Kouzarides, 2007). Identification of the chromatin regulatory proteins involved in mediating, removing, and binding these modifications has expedited our understanding of the biology of many of these PTMs (Figure 1). Moreover, examining the genome-wide localization of histone PTMs, DNA methylation, and chromatin regulatory proteins in a wide spectrum of biological contexts has allowed researchers to begin defining "epigenomic landscapes" and how these relate to cellular phenotypes (Bernstein et al., 2010). Combining these data with gene-expression profiles has provided significant insights into the biological significance of many of these entities as they relate to gene expression (Brien and Bracken, 2009).

It has been appreciated for some time that deregulation of the epigenomic landscape is a common feature of a number of diseases, including cancer. Some of the earliest observed epigenetic abnormalities in cancer cells were alterations in the patterns of DNA methylation and histone acetylation (Feinberg and Vogelstein, 1983; Fraga et al., 2005; Greger et al., 1989; Sakai et al., 1991). Localized hypermethylation of gene-promoter regions leading to transcriptional repression of tumor-suppressor genes such as *CDKN2A* and *RB1* were subsequently found to be a common feature of many cancers (Baylin and Jones, 2011). Moreover, DNA hypermethylation events also occur over broad subchromosomal domains encompassing multiple tumor-suppressor genes (Coolen et al., 2010; Frigola et al., 2006). The chemotherapeutic agents azacitidine (5-azacytidine) and decitabine (5-aza-2′-deoxycytidine), when used at low doses, were shown to irreversibly inhibit the enzymatic activity of the DNA methyltransferase enzyme DNMT1 and induce global hypomethylation. These drugs represent the first targeted epigenetic therapies and were approved by the Food and Drug Administration (FDA) in 2005 for the treatment of myelodysplastic syndrome (MDS), and are currently recommended as first-line treatments for high-risk MDS patients (Issa and Kantarjian, 2009). Global loss of histone acetylation is also a common feature of many cancers (Fraga et al., 2005), and has been associated with unfavorable patient outcomes in certain cases (Seligson et al., 2005). Vorinostat (suberoylanilide hydroxamic acid [SAHA]), which inhibits the activity of histone deacetylase (HDAC) enzymes, leading to global increases in histone acetylation, was granted FDA approval for the treatment of advanced cutaneous T cell lymphoma in 2006 (Mann et al., 2007; Wagner et al., 2010). Since this initial success, the HDAC inhibitors romidepsin and panobinostat have been approved for use in cutaneous T cell lymphoma and multiple myeloma, respectively (Khan and La Thangue, 2012; Laubach et al., 2015). Recently, studies that combine DNA methylation and HDAC inhibitors


CrossMark

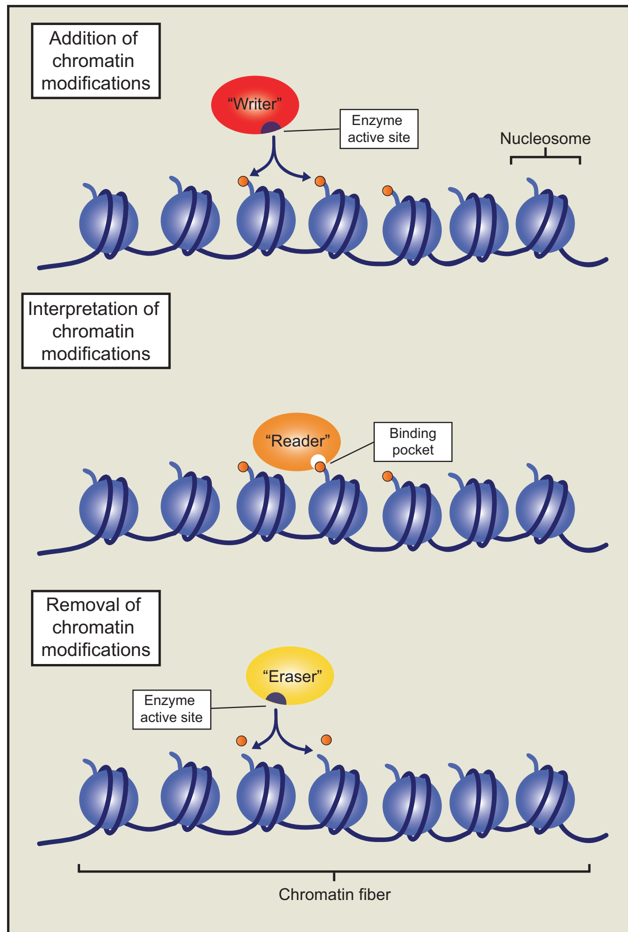


**Figure 1. Chromatin Writers, Readers, and Erasers in Epigenetic Gene Regulation**
The addition of histone post-translational modifications is catalyzed by a class of enzymes known as chromatin "writers." The modifications established by these writers (denoted by the orange circle) may affect gene transcription by altering electrostatic interactions within or between adjacent nucleosomes. Alternatively they may act as binding substrates for another class of chromatin regulators called chromatin "readers." Chromatin readers employ characteristic binding domains, such as chromo-, bromo-, and PHD-finger domains to bind nucleosomes marked by specific modifications, or a combination of modifications. Chromatin readers may themselves possess additional chromatin-modifying activities, or alternatively recruit additional proteins to modify the local chromatin environment. Finally, chromatin "erasers" catalyze the removal of histone modifications, thereby reversing their biochemical effects on the chromatin fiber.

have been initiated, with several clinical trials currently ongoing examining the utility of these combinations in hematopoietic malignancies and solid tumors (Falkenberg and Johnstone, 2014). Moreover, pre-clinical studies have indicated that combination therapies involving HDAC inhibitors and some of the emerging epigenetic therapies may prove clinically beneficial (Fiskus et al., 2014; Mazur et al., 2015).

Until recently it was unclear whether epigenetic changes play a causal role in cancer development or whether they merely are a result of the cancerous state. However, recent cancer genome-sequencing studies have shown that genes encoding chromatin regulatory proteins are among the most commonly mutated gene sets in cancer (Garraway and Lander, 2013). In fact, 25%–30% of the identified cancer driver mutations affect genes encoding chromatin regulatory proteins (Garraway and Lander, 2013; Vogelstein et al., 2013). These findings indicate that altered epigenetic states do not just correlate with cancer but likely drive disease pathogenesis. This has spurred a significant research effort to understand how altered epigenetic states drive cancer cell phenotypes and how to therapeutically exploit these phenomena. We have only begun to scratch the surface with regard to our mechanistic understanding of the cancer epigenome, but this limited knowledge has already delivered tangible successes with regard to our ability to therapeutically manipulate cancer-promoting epigenetic states and cancer-associated gene-expression programs (Table 1) (Cai et al., 2015).

In this perspective, we discuss how our burgeoning understanding of the cancer epigenome and chromatin regulatory mechanisms are yielding significant insights into the mechanisms underlying disease development, and providing a rational means to identify drug targets for the treatment of certain cancers. This is a very exciting time in the field, with a number of targeted epigenetic therapies in ongoing clinical trials. However, the relatively small number of drug targets identified to date is still a limiting factor, and we will also discuss how a more comprehensive approach to studying the cancer epigenome will be necessary in order to truly harness the therapeutic potential therein.

## Exploiting Oncogenic Chromatin Activities

### *Oncogenic Chromatin Writers*

The histone methyltransferase (HMT) EZH2 is subject to recurrent gain-of-function mutations in B cell lymphoma (Morin et al., 2010, 2011). EZH2 is a lysine methyltransferase and the catalytic subunit of the PRC2 complex; as part of this complex, EZH2 mediates the mono-, di-, and trimethylation of lysine 27 of histone H3 (H3K27me1/2/3) (Conway et al., 2015). EZH2 primarily functions as a transcriptional repressor through deposition of H3K27me3 at the promoter regions of PRC2 target genes (Margueron and Reinberg, 2011). In addition, EZH2 mediated H3K27me2 may also be important for transcriptional repression by maintaining the inactive state of intergenic enhancer elements (Ferrari et al., 2014; Lee et al., 2015). Heterozygous point mutations of *EZH2* are found in 22% of diffuse large B cell lymphoma cases and 10% of follicular lymphoma cases. These mutations affect key residues within the active site of the catalytic Su(var) 3-9, enhancer of zeste, trithorax (SET) domain (McCabe et al., 2012a; Morin et al., 2010). In vitro analysis has shown that the preferred enzymatic activity of wild-type EZH2 is the conversion of H3K27me0 to H3K27me1 and H3K27me1 to H3K27me2, while the enzyme is relatively inefficient at the final conversion step to H3K27me3. However, owing to alterations in substrate binding modality, the lymphoma associated EZH2 SET domain mutants exhibit an enhanced ability to convert H3K27me2 to H3K27me3 (Antonysamy et al., 2013; McCabe et al., 2012a; Sneeringer et al., 2010; Wigle et al., 2011; Yap et al., 2011). This finding suggests that wild-type and mutant EZH2 collaborate to push the kinetics of PRC2 activity toward increased H3K27me3 production. Indeed, lymphoma cell lines containing *EZH2* gain-of-function mutations exhibit globally increased levels of H3K27me3, with a concomitant decrease in H3K27me2 (McCabe et al., 2012a, 2012b; Yap et al., 2011). Chromatin immunoprecipitation coupled with next-generation

Download English Version:

https://daneshyari.com/en/article/2106770

Download Persian Version:

https://daneshyari.com/article/2106770

Daneshyari.com