Published in final edited form as:

Prog Biophys Mol Biol. 2015 July ; 118(0): 8–13. doi:10.1016/j.pbiomolbio.2015.02.013.

Phosphorylation of Epigenetic “Readers, Writers and Erasers”: Implications for Developmental Reprogramming and the Epigenetic Basis for Health and Disease

Lindsey S. Treviño, Quan Wang, and Cheryl L. Walker

Center for Translational Cancer Research, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, TX, USA

Abstract

Epigenetic reprogramming that occurs during critical periods of development can increase the susceptibility to many diseases in adulthood. Programming of the epigenome during development occurs via the activity of a variety of epigenetic modifiers, including “readers, writers and erasers” of histone methyl marks. Posttranslational modification of these programmers can alter their activity, resulting in global or gene-specific changes in histone methylation and gene transcription. This review summarizes what is currently known about phosphorylation of histone methyltransferases (“writers”), demethylases (“erasers”) and effector proteins (“readers”) that program the epigenome, and the impact of this posttranslational modification on their activity. Understanding how the activity of these epigenetic programmers is perturbed by environmental exposures via changes in phosphorylation is key to understanding mechanisms of developmental reprogramming and the epigenetic basis of health and disease.

Keywords

Developmental reprogramming; phosphorylation; histone modifiers; cancer

1. Introduction

“Epigenetics” is typically defined as “heritable changes in gene expression that are not caused by alterations in DNA sequence”. Epigenetic programming plays an essential role in health and disease, from fertilization to death, regulating the differentiation and functionality of all cell types. Throughout life, although the epigenome retains plasticity, it is dynamically and tightly regulated in response to intrinsic and environmental signals to properly direct gene expression and cell function. Dysregulation of these epigenetic programs is linked to many human diseases including metabolic diseases and cancer, as well as neurological and reproductive function (Walker and Ho, 2012).

Corresponding Author: Cheryl L. Walker; Address: 2121 W. Holcombe Blvd, Houston, TX 77030; Phone: 713-677-7440; cwalker@ibt.tamhsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Changes in epigenetic programs occur in response to alterations in DNA methylation patterns, changes in histone modifications, and altered expression of non-coding RNAs, which together regulate chromatin architecture and gene transcription. Epigenetic modifiers, those that add ('writers') or remove ("erasers") DNA or histone modifications or which recognize, bind, and affect epigenetic programs in response to specific epigenetic modifications ('readers'), have emerged as key epigenetic programmers. While "writers" and "erasers" modulate the epigenetic code on DNA and histones, the code itself serves as a platform to recruit effector proteins or "readers" that interpret the code and determine the final biological outcome.

Accumulating data now show that these epigenetic programmers are targets for posttranslational modifications (PTMs) that can regulate their activity. In this article, we will focus on the importance of a specific PTM, phosphorylation, and the regulation of the "readers, writers and erasers" of epigenetic histone methyl marks. We provide a summary of the known sites for phosphorylation of histone modifying proteins, along with a discussion of how phosphorylation regulates their activity. Finally, we will discuss regulation of histone modifying proteins by extrinsic stimuli in some well-established environmental exposure settings. These data lay the groundwork for understanding how PTMs (specifically phosphorylation) of histone modifiers contributes to epigenetic reprogramming that occurs in response to adverse environmental exposures during critical developmental periods to increase susceptibility to many diseases in adulthood.

2. Regulation of epigenetic programmers by phosphorylation

The activity of epigenetic "readers, writers and erasers" of histone methyl marks can be regulated by PTMs, including phosphorylation, ubiquitination, and sumoylation. This review will focus on the phosphorylation by kinases activated in cell signaling pathways of histone methyltransferases ("writers"), demethylases ("erasers") and effector proteins ("readers") that program the epigenome. Table 1 summarizes the known phosphorylation sites of the methyltransferases, demethylases and associated effector proteins. Phosphorylation of these "readers, writers and erasers" is known to be mediated by a variety of kinases including protein kinase B (PKB/Akt), cyclin-dependent kinases (CDKs), protein kinase A (PKA), casein kinase 2 (Ck2) and ataxia telangiectasia and Rad3 related kinase (ATR).

Identification of the kinase responsible for a specific phosphorylation event is generally determined using *in vitro* kinase assays, cell culture studies with selective kinase activators and/or inhibitors, and phosphorylation site-specific target protein mutants. In some cases, phosphorylation is observed without identification of the responsible kinase, for example in using proteomic and mass spectrometry approaches. Although the list is growing of specific sites of phosphorylation on epigenetic "readers, writers and erasers" of histone methyl marks, the functional consequences of these modifications are still largely unknown.

Regulation of activity by phosphorylation may occur directly, via activation/inactivation of enzymatic activity, or indirectly by regulating modifier interaction with other proteins (or RNAs) or binding to chromatin. Regulation of activity via phosphorylation has been shown for several epigenetic programmers, including enhancer of Zeste homolog 2 (EZH2),

euchromatic histone-lysine-N-methyltransferase 2 (EHMT2/G9a), mixed-lineage leukemia protein 1 (MLL), SET domain bifurcated 1 (SETDB1), Su(var)3-9 homolog 1 (SUV39H1) and lysine-specific histone demethylase 1A (LSD1), which have been implicated in the etiology of a variety of cancers (reviewed in (Decarlo and Hadden, 2012)).

2.1 Phosphorylation that decreases methyltransferase (“writer”) activity

Phosphorylation of the histone H3 lysine 27 trimethyl (H3K27me3) methyltransferase EZH2 on serine 21 by Akt has been shown to inhibit its activity (Cha et al., 2005). This decreased activity results in decreased expression of the H3K27me3 repressive mark (Bredfeldt et al., 2010; Cha et al., 2005), increased expression of genes normally silent in target tissues (Cha et al., 2005) and is associated with increased hormone-responsiveness of estrogen-responsive genes (Bredfeldt et al., 2010; Greathouse et al., 2012). In the setting of early life exposures to xenoestrogens, which activate PI3K/AKT and induce EZH2 phosphorylation on serine 21, developmental reprogramming by neonatal xenoestrogen exposure decreases EZH2 activity, results in loss of the repressive H3K27me3 mark, and increases risk for uterine tumorigenesis (Bredfeldt et al., 2010; Greathouse et al., 2012).

Oncogenic Janus kinase 2 (JAK2V617F) phosphorylates protein arginine methyltransferase 5 (PRMT5) on several tyrosine residues, resulting in decreased enzymatic activity (Liu et al., 2011), which would result in loss of repressive marks added by PRMT5 and increased gene expression (Di Lorenzo and Bedford, 2011). The activity of coactivator-associated arginine methyltransferase (CARM1) is negatively regulated by phosphorylation at serine 217 (Feng et al., 2009) and at serine 228 (Higashimoto et al., 2007), although the kinase(s) responsible have not been identified. Inactivation of CARM1 would be predicted to decrease gene transcription, as the histone H3 arginine 17 (H3R17) methyl mark is associated with activation of gene transcription (Bauer et al., 2002), and CARM1 is a co-activator for other transcription factors, including the estrogen receptor (Chen et al., 2000).

Site-specific phosphorylation of epigenetic modifier proteins can also modulate protein-protein interactions that would ultimately decrease activity. For example, phosphorylation of EZH2 on threonine 487 by CDK1 decreases binding of EZH2 to other components of the polycomb repressive complex 2 (PRC2), resulting in decreased methyltransferase activity (Wei et al., 2011). As a result, levels of the repressive H3K27me3 histone methyl mark would decrease, increasing gene expression (Figure 1).

2.2 Phosphorylation that increases methyltransferase (“writer”) activity

ATR phosphorylates the H3K4 methyltransferase MLL on serine 516 disrupting its interaction with, and ultimate degradation by, the S-phase kinase-associated protein 2 (Skp2) E3 ubiquitin ligase (Liu et al., 2010a). In the case of MLL, a methyltransferase in the COMPASS complex (Smith et al., 2011), stabilization is predicted to increase gene transcription by increasing levels of the H3K4me3 active histone methyl mark (Figure 1).

Site-specific phosphorylation of epigenetic programmers can modulate binding of methyltransferases to target loci on DNA thereby enhancing activity. For example, phosphorylation of EZH2 on threonine 350 by CDK1/CDK2 increases EZH2 recruitment to, and maintenance of, H3K27me3 levels at target loci, enhancing global gene silencing (Chen

et al., 2010). Neuro-like kinase (NLK) phosphorylates the H3K9 methyltransferase SETDB1 on threonine 976, which increases SETDB1 binding to chromodomain helicase DNA binding protein (CHD) and subsequent SETDB1 recruitment to target loci (Takada et al., 2007). Phosphorylation of SETDB1 at this site results in an increase in the H3K9me3 repressive mark, which would decrease gene transcription (Figure 2).

Although the aforementioned studies have shed light on how phosphorylation can modulate the activity of methyltransferases, many questions remain. Clearly there are likely to be additional functional consequences for these, and other phosphorylation events, which are yet to be identified. For example, it has been reported that CDK1-dependent phosphorylation of EZH2 increases EZH2 binding to ncRNA, although the physiological consequence of this phosphorylation is still unknown (Kaneko et al., 2010).

2.3 Phosphorylation can modify the activity of “readers and erasers”

Less is known about how phosphorylation regulates the activity of demethylases and effector proteins; however, these epigenetic programmers also appear to be targets for regulatory phosphorylation. PKA-mediated phosphorylation of the H3K9 dimethyl (H3K9me2) demethylase PHD finger protein 2 (PHF2) on serine 1056 increases its enzymatic activity (Baba et al., 2011). As H3K9me2 is a repressive mark, increased PHF2 activity would be predicted to decrease gene transcription (Wang et al., 2008). Phosphorylation of the demethylase PHD finger protein 8 (PHF8) by CDK1 on serines 33 and 84 regulates dismissal of PHF8 from chromatin (Arteaga et al., 2013; Liu et al., 2010a), and may result in sustained gene silencing since PHF8-mediated removal of repressive marks does not occur.

Phosphorylation of the histone reader heterochromatin protein 1 gamma (HP1 γ) on serine 83 by PKA promotes its interaction with Ku70 and impairs its silencing activity (Figure 3) (Lomber et al., 2006), and Ck2-mediated phosphorylation of HP1-beta on threonine 51 results in the dismissal of HP1-beta from chromatin, chromatin remodeling, and initiation of the DNA damage response (Ayoub et al., 2008).

3. Histone methyl marks as targets for environmental carcinogens

Studies in humans and animal models have pointed to an association between epigenetic changes in histone modifications and many diseases, with associations found with histone methyl (or acetyl) marks at the global chromatin level, as well as associated with individual genes. For example, changes in histone methylation have been reported in normal mammary gland epithelial cells, as well as breast cancer cells exposed to xenoestrogens (Bredfeldt et al., 2010; Doherty et al., 2010) and polycyclic aromatic hydrocarbons (PAHs) (Bradley et al., 2007; Sadikovic et al., 2008). In addition, xenoestrogen-mediated alterations in histone methylation have been associated with uterine tumorigenesis (Greathouse et al., 2012). Exposure to heavy metals such as arsenic and nickel is associated with lung carcinogenesis and these metals can regulate histone methylation (reviewed in (Cheng et al., 2012)). Furthermore, alterations in histone methylation have been observed in cells exposed to tobacco-smoke condensate, which promotes tumorigenesis (Hussain et al., 2009). Thus along with DNA methylation, which has long been known to be a target for epigenetic

alterations involved in many types of cancer, epigenetic alterations in histone methylation are now also thought to be an important target for environmental carcinogens. However, while there is growing evidence that environmental exposures have the potential to alter histone (and other types of) methylation, few studies have examined the molecular mechanisms by which exposure to environmental agents influence the activity of epigenetic programmers. The best examples, to date, of activation of kinases to phosphorylate and modify the activity of epigenetic programmers are early life exposures to environmental agents that reprogram the epigenome to increase susceptibility to cancer later in life.

The exposure of tissues or organs to an adverse environment during critical developmental periods can increase susceptibility to many diseases in adulthood such as cardiovascular disease, obesity and cancer (Barker, 2012; Jirtle and Skinner, 2007). The developmental origins of health and disease (DOHaD) hypothesis has led to the understanding that adverse exposures during development can reprogram the response to normal physiologic signals in a way that leads to lifelong changes in disease susceptibility (Barker, 2007; Walker and Ho, 2012).

Studies from our lab were the first to show that activation of cell signaling pathways and phosphorylation of epigenetic programmers during critical periods of development altered their activity and reprogramed the epigenome to increase cancer risk in adulthood. We demonstrated that neonatal exposure to the xenoestrogens diethylstilbestrol (DES) or genistein activates non-genomic PI3K/Akt signaling in the rat uterus, resulting in increased phosphorylation at serine 21 of the methyltransferase EZH2 and a subsequent decrease in H3K27me3 levels in this tissue (Bredfeldt et al., 2010; Greathouse et al., 2012). Interestingly, activation of non-genomic signaling and repression of EZH2 activity exhibits both xenoestrogen- and tissue-specificity. In contrast to DES and genistein, another xenoestrogen, bisphenol A (BPA) failed to activate non-genomic signaling in the uterus and did not modulate EZH2 activity, although BPA was able to induce non-genomic signaling to phosphorylate EZH2 in the developing prostate (Greathouse et al., 2012). Both DES and genistein (but not BPA) developmentally reprogrammed gene expression, increasing both the hormone responsiveness of estrogen-responsive genes in the adult uterus, and the incidence of hormone-dependent uterine tumors (Bredfeldt et al., 2010; Cook et al., 2005; Greathouse et al., 2012). While this work constitutes a clear example of a specific signaling pathway (PI3K/AKT) engaging a specific epigenetic programmer (EZH2) and directing site-specific phosphorylation (S21), much work remains to be done to demonstrate if non-genomic signaling as a mediator of epigenetic reprogramming is generalizable to other signaling pathways and kinases, epigenetic programmers, and diseases. It is clear that we have yet to fully unravel the link between PTMs of epigenetic programmers, reprogramming of the epigenome, and the developmental origins of health and disease.

Conclusions

We are just beginning to understand how posttranslational modification of epigenetic programmers contributes to developmental reprogramming by environmental exposures that increase susceptibility to disease. Prediction algorithms indicate that the methyltransferases, demethylases and effector proteins discussed above, as well other epigenetic programmers

not discussed, have numerous sites with the potential to serve as substrate for multiple kinases, setting the stage for combinatorial regulatory phosphorylation events. Epigenetic programmers are targeted for other PTMs in addition to phosphorylation, although the crosstalk between multiple and combinatorial modifications on their activity remains to be investigated. Thus, regulation of epigenetic programmers by cell signaling pathways will undoubtedly be complex, and further study is clearly needed.

In recent years, there has been a rapid rise in the prevalence of non-communicable diseases that are now recognized as major challenges to public health globally (reviewed in (Hanson and Gluckman, 2014)). Understanding how environmental exposures regulate epigenetic programmers is anticipated to yield unique and valuable insights into the mechanisms responsible for many of these, including those linked to environmental exposures such as cardiovascular disease, metabolic diseases such as obesity and diabetes, and cancer. Accordingly, elucidating the epigenetic basis for the developmental origins of health and disease is now an exciting new frontier in human environmental health research.

Acknowledgments

C.L.W. is supported by grants from the Cancer Prevention Research Institute of Texas (CPRIT; RP120855), the Robert Welch Foundation (BE-0023) and the National Institutes of Health (RC2 ES018789-02 and R01 ES008263-14).

References

- Arteaga MF, Mikesch JH, Qiu J, Christensen J, Helin K, Kogan SC, Dong S, So CW. The histone demethylase PHF8 governs retinoic acid response in acute promyelocytic leukemia. *Cancer Cell*. 2013; 23:376–389. [PubMed: 23518351]
- Ayoub N, Jeyasekharan AD, Bernal JA, Venkitaraman AR. HP1-beta mobilization promotes chromatin changes that initiate the DNA damage response. *Nature*. 2008; 453:682–686. [PubMed: 18438399]
- Baba A, Ohtake F, Okuno Y, Yokota K, Okada M, Imai Y, Ni M, Meyer CA, Igarashi K, Kanno J, Brown M, Kato S. PKA-dependent regulation of the histone lysine demethylase complex PHF2-ARID5B. *Nat Cell Biol*. 2011; 13:668–675. [PubMed: 21532585]
- Barker DJ. The origins of the developmental origins theory. *J Intern Med*. 2007; 261:412–417. [PubMed: 17444880]
- Barker DJ. Sir Richard Doll Lecture. Developmental origins of chronic disease. *Public Health*. 2012; 126:185–189. [PubMed: 22325676]
- Bauer UM, Daujat S, Nielsen SJ, Nightingale K, Kouzarides T. Methylation at arginine 17 of histone H3 is linked to gene activation. *EMBO Rep*. 2002; 3:39–44. [PubMed: 11751582]
- Boeke J, Regnard C, Cai W, Johansen J, Johansen KM, Becker PB, Imhof A. Phosphorylation of SU(VAR)3–9 by the chromosomal kinase JIL-1. *PLoS One*. 2010; 5:e10042. [PubMed: 20386606]
- Bradley C, van der Meer R, Roodi N, Yan H, Chandrasekharan MB, Sun ZW, Mernaugh RL, Parl FF. Carcinogen-induced histone alteration in normal human mammary epithelial cells. *Carcinogenesis*. 2007; 28:2184–2192. [PubMed: 17468514]
- Bredfeldt TG, Greathouse KL, Safe SH, Hung MC, Bedford MT, Walker CL. Xenoestrogen-induced regulation of EZH2 and histone methylation via estrogen receptor signaling to PI3K/AKT. *Mol Endocrinol*. 2010; 24:993–1006. [PubMed: 20351197]
- Cha TL, Zhou BP, Xia W, Wu Y, Yang CC, Chen CT, Ping B, Otte AP, Hung MC. Akt-mediated phosphorylation of EZH2 suppresses methylation of lysine 27 in histone H3. *Science*. 2005; 310:306–310. [PubMed: 16224021]

- Chen D, Huang SM, Stallcup MR. Synergistic, p160 coactivator-dependent enhancement of estrogen receptor function by CARM1 and p300. *J Biol Chem*. 2000; 275:40810–40816. [PubMed: 11010967]
- Chen S, Bohrer LR, Rai AN, Pan Y, Gan L, Zhou X, Bagchi A, Simon JA, Huang H. Cyclin-dependent kinases regulate epigenetic gene silencing through phosphorylation of EZH2. *Nat Cell Biol*. 2010; 12:1108–1114. [PubMed: 20935635]
- Cheng TF, Choudhuri S, Muldoon-Jacobs K. Epigenetic targets of some toxicologically relevant metals: a review of the literature. *J Appl Toxicol*. 2012; 32:643–653. [PubMed: 22334439]
- Cook JD, Davis BJ, Cai SL, Barrett JC, Conti CJ, Walker CL. Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. *Proc Natl Acad Sci U S A*. 2005; 102:8644–8649. [PubMed: 15937110]
- Decarlo D, Hadden MK. Oncoepigenomics: making histone lysine methylation count. *Eur J Med Chem*. 2012; 56:179–194. [PubMed: 22975593]
- Di Lorenzo A, Bedford MT. Histone arginine methylation. *FEBS Lett*. 2011; 585:2024–2031. [PubMed: 21074527]
- Doherty LF, Bromer JG, Zhou Y, Aldad TS, Taylor HS. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: an epigenetic mechanism linking endocrine disruptors to breast cancer. *Horm Cancer*. 2010; 1:146–155. [PubMed: 21761357]
- Feng Q, He B, Jung SY, Song Y, Qin J, Tsai SY, Tsai MJ, O'Malley BW. Biochemical control of CARM1 enzymatic activity by phosphorylation. *J Biol Chem*. 2009; 284:36167–36174. [PubMed: 19843527]
- Greathouse KL, Bredfeldt T, Everitt JI, Lin K, Berry T, Kannan K, Mittelstadt ML, Ho SM, Walker CL. Environmental estrogens differentially engage the histone methyltransferase EZH2 to increase risk of uterine tumorigenesis. *Mol Cancer Res*. 2012; 10:546–557. [PubMed: 22504913]
- Hanson MA, Gluckman PD. Developmental origins of health and disease - Global public health implications. *Best Pract Res Clin Obstet Gynaecol*. 2014
- Higashimoto K, Kuhn P, Desai D, Cheng X, Xu W. Phosphorylation-mediated inactivation of coactivator-associated arginine methyltransferase 1. *Proc Natl Acad Sci U S A*. 2007; 104:12318–12323. [PubMed: 17640894]
- Hussain M, Rao M, Humphries AE, Hong JA, Liu F, Yang M, Caragacianu D, Schrupp DS. Tobacco smoke induces polycomb-mediated repression of Dickkopf-1 in lung cancer cells. *Cancer Res*. 2009; 69:3570–3578. [PubMed: 19351856]
- Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet*. 2007; 8:253–262. [PubMed: 17363974]
- Kaneko S, Li G, Son J, Xu CF, Margueron R, Neubert TA, Reinberg D. Phosphorylation of the PRC2 component Ezh2 is cell cycle-regulated and up-regulates its binding to ncRNA. *Genes Dev*. 2010; 24:2615–2620. [PubMed: 21123648]
- Liang CY, Hsu PH, Chou DF, Pan CY, Wang LC, Huang WC, Tsai MD, Lo WS. The histone H3K36 demethylase Rph1/KDM4 regulates the expression of the photoreactivation gene PHR1. *Nucleic Acids Res*. 2011; 39:4151–4165. [PubMed: 21296759]
- Liu F, Zhao X, Perna F, Wang L, Koppikar P, Abdel-Wahab O, Harr MW, Levine RL, Xu H, Tefferi A, Deblasio A, Hatlen M, Menendez S, Nimer SD. JAK2V617F-mediated phosphorylation of PRMT5 downregulates its methyltransferase activity and promotes myeloproliferation. *Cancer Cell*. 2011; 19:283–294. [PubMed: 21316606]
- Liu H, Takeda S, Kumar R, Westergard TD, Brown EJ, Pandita TK, Cheng EH, Hsieh JJ. Phosphorylation of MLL by ATR is required for execution of mammalian S-phase checkpoint. *Nature*. 2010a; 467:343–346. [PubMed: 20818375]
- Liu W, Tanasa B, Tyurina OV, Zhou TY, Gassmann R, Liu WT, Ohgi KA, Benner C, Garcia-Bassets I, Aggarwal AK, Desai A, Dorrestein PC, Glass CK, Rosenfeld MG. PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression. *Nature*. 2010b; 466:508–512. [PubMed: 20622854]
- Lomberk G, Bensi D, Fernandez-Zapico ME, Urrutia R. Evidence for the existence of an HP1-mediated subcode within the histone code. *Nat Cell Biol*. 2006; 8:407–415. [PubMed: 16531993]

- Park SH, Yu SE, Chai YG, Jang YK. CDK2-dependent phosphorylation of Suv39H1 is involved in control of heterochromatin replication during cell cycle progression. *Nucleic Acids Res.* 2014; 42:6196–6207. [PubMed: 24728993]
- Sadikovic B, Andrews J, Carter D, Robinson J, Rodenhiser DI. Genome-wide H3K9 histone acetylation profiles are altered in benzopyrene-treated MCF7 breast cancer cells. *J Biol Chem.* 2008; 283:4051–4060. [PubMed: 18065415]
- Sampath SC, Marazzi I, Yap KL, Sampath SC, Krutchinsky AN, Mecklenbrauker I, Viale A, Rudensky E, Zhou MM, Chait BT, Tarakhovsky A. Methylation of a histone mimic within the histone methyltransferase G9a regulates protein complex assembly. *Mol Cell.* 2007; 27:596–608. [PubMed: 17707231]
- Smith E, Lin C, Shilatifard A. The super elongation complex (SEC) and MLL in development and disease. *Genes Dev.* 2011; 25:661–672. [PubMed: 21460034]
- Takada I, Mihara M, Suzawa M, Ohtake F, Kobayashi S, Igarashi M, Youn MY, Takeyama K, Nakamura T, Mezaki Y, Takezawa S, Yogiashi Y, Kitagawa H, Yamada G, Takada S, Minami Y, Shibuya H, Matsumoto K, Kato S. A histone lysine methyltransferase activated by non-canonical Wnt signalling suppresses PPAR- γ transactivation. *Nat Cell Biol.* 2007; 9:1273–1285. [PubMed: 17952062]
- Toffolo E, Rusconi F, Paganini L, Tortorici M, Pilotto S, Heise C, Verpelli C, Tedeschi G, Maffioli E, Sala C, Mattevi A, Battaglioli E. Phosphorylation of neuronal Lysine-Specific Demethylase LSD1/KDM1A impairs transcriptional repression by regulating interaction with CoREST and histone deacetylases HDAC1/2. *J Neurochem.* 2014; 128:603–616. [PubMed: 24111946]
- Walker CL, Ho SM. Developmental reprogramming of cancer susceptibility. *Nat Rev Cancer.* 2012; 12:479–486. [PubMed: 22695395]
- Wang Z, Zang C, Rosenfeld JA, Schones DE, Barski A, Cuddapah S, Cui K, Roh TY, Peng W, Zhang MQ, Zhao K. Combinatorial patterns of histone acetylations and methylations in the human genome. *Nat Genet.* 2008; 40:897–903. [PubMed: 18552846]
- Wei Y, Chen YH, Li LY, Lang J, Yeh SP, Shi B, Yang CC, Yang JY, Lin CY, Lai CC, Hung MC. CDK1-dependent phosphorylation of EZH2 suppresses methylation of H3K27 and promotes osteogenic differentiation of human mesenchymal stem cells. *Nat Cell Biol.* 2011; 13:87–94. [PubMed: 21131960]
- Wu S, Wang W, Kong X, Congdon LM, Yokomori K, Kirschner MW, Rice JC. Dynamic regulation of the PR-Set7 histone methyltransferase is required for normal cell cycle progression. *Genes Dev.* 2010; 24:2531–2542. [PubMed: 20966048]
- Zhao C, Nguyen T, Yusifov T, Glasgow BJ, Lehrer RI. Lipophilins: human peptides homologous to rat prostatein. *Biochem Biophys Res Commun.* 1999; 256:147–155. [PubMed: 10066439]

Figure 1.

Nongenomic signaling pathways that modulate the activity of epigenetic “writers” resulting in increased gene expression. Activated CDK1 phosphorylates and inhibits EZH2 binding to other components of the PRC2 complex, which leads to a decrease in EZH2 activity. Activated ATR phosphorylates and inhibits MLL binding to the E3 ubiquitin ligase Skp2, resulting in increased MLL expression and activity.

Figure 2. Nongenomic signaling pathways that modulate the activity of epigenetic “writers” resulting in decreased gene expression. Activated NLK phosphorylates SETDB1, which leads to SETB1 binding to CHD and recruitment to target loci.

Figure 3. Nongenomic signaling pathways that modulate the activity of epigenetic “readers” resulting in increased gene expression. Activated PKA phosphorylates HP1γ enhancing its interaction with Ku70 and impairing its silencing activity.

Table 1

Known modifications of epigenetic “writers, erasers 1 and “readers”.

Name	Protein Function	Modification site	Upstream Kinase(s)	Effect	Physiological relevance	Reference
Writers						
CARM1	H3K27/17/26 arginine methyltransferase	Ser 217	ND	Decreased activity and altered localization	ND	(Feng et al., 2009)
		Ser 228	ND	Decreased activity	Decreased coactivation of ER target genes	(Higashimoto et al., 2007)
		Ser 21	Akt	Decreased activity	ND	(Cha et al., 2005)
					Developmental reprogramming	(Bredfeldt et al., 2010)
					Increased risk of uterine tumorigenesis	(Greathouse et al., 2012)
EZH2	H3K27 methyltransferase	Thr 345, 487	CDK1	Increased binding to ncRNA	ND	(Kaneko et al., 2010)
		Thr 350	CDK1, CDK2	Recruitment to target loci	Increased tumor-promoting function	(Chen et al., 2010)
		Thr 487	CDK1	Decreased binding to PRC2 components	Promotes differentiation of mesenchymal stem cells	(Wei et al., 2011)
G9A	H3K9 methyltransferase	Thr 166	Aurora B	Antagonizes binding to HP1 γ	ND	(Sampath et al., 2007)
MLL	H3K4 methyltransferase	Ser 516	ATR	Decreased Skp2-mediated degradation	Promotion of the pathogenesis of MLL leukemias	(Liu et al., 2010a)
PRMT5	H4 and H2A arginine methyltransferase	Tyr 297/304/307	JAK2V617F	Decreased activity	Promotes myeloproliferation	(Liu et al., 2011)
PR-Set7 (SET8)	H4K20 methyltransferase	Ser 29	CDK1	Altered chromatin binding	Regulates cell cycle progression	(Wu et al., 2010)
SETDB1	H3K9 methyltransferase	Thr 976	NLK	Increased interaction with CHD and recruitment to target loci	Suppresses PPAR γ and promotes differentiation of mesenchymal stem cells	(Takada et al., 2007)
SUV39H1	H3K9 methyltransferase	Ser 391	CDK2	Altered chromatin binding	Initiation of heterochromatin replication	(Park et al., 2014)
SU(VAR)3-9	H3K9 methyltransferase	Ser 191	JIL-1	ND	ND	(Boeke et al., 2010)
Erasers						

Name	Protein Function	Modification site	Upstream Kinase(s)	Effect	Physiological relevance	Reference
LSD1	H3K4 and H3K9 demethylase	Thr 369b	ND	Decreased binding to corepressors	Promotes morphogenesis in cortical neurons	(Toffolo et al., 2014)
PHF2	H3K9 demethylase	Ser 1056	PKA	Increased activity	Coactivation of HNF4 target genes	(Baba et al., 2011)
PHF8	H3K9, H3K27, and H4K20 demethylase	Ser 33, 84	CDK1	Altered chromatin binding	Regulates cell cycle progression	(Liu et al., 2010b)
					Mediates ATRA response in leukemia	(Arteaga et al., 2013)
Rph1/KDM4	H3K36 demethylase	Ser 652	Rad53	Regulation of PHR1 gene expression	ND	(Liang et al., 2011)
Readers						
HP1	H3K9	Ser 15, Ser 202	Ck2	Altered binding to target proteins in heterochromatin	ND	(Zhao et al., 1999)
HP1 β	H3K9	Thr 51	Ck2	Altered chromatin binding	ND	(Ayoub et al., 2008)
HP1 γ	H3K9	Ser 83	PKA	Increased binding to Ku70	ND	(Lomber et al., 2006)