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Methylation in Tumorigenesis

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1. Introduction

The development, maturation, and maintenance of tissues and organisms are anchored in distinct programs for protein expression which define the identities and roles of individual cell lines [1, 2]. These programs are maintained in a heritable state by epigenetic mechanisms that convey cellular memory [3, 4]. In this way, the global synchronization of patterns in gene expression broadly dictates developmental consequences [5, 6]. At the foundation of such gene regulation are coordinated cascades that affect the packaging of DNA into chromatin, thereby establishing the degree of DNA accessibility to transcriptional complexes [7-10]. These pathways include histone methylation, methylation of transcriptional regulators, DNA methylation, histone replacement, chromatin remodeling, and other alterations to histone tails [11-16]. Abnormalities in these epigenetic events are commonly associated with tumorigenesis and subsequent clinical outcomes [17-23].

From tightly regulated transcription to mitosis, chromatin is an elastic repository of the genome [24]. In this state, a chromosome is sequentially condensed through a succession of organized compaction while limited regions of DNA are selectively made available to transcriptional complexes [25, 26]. Hence, chromatin exists in a dynamic state into which approximately 2 m of DNA is packaged in the nucleus while maintaining an extraordinary level of utility [25, 26]. At its core, chromatin is established in a series of nucleosomes, their basic structural unit [25, 27], comprised of 146 base pairs of DNA, wrapped 1.7 times around an octamer of histones and interspersed by regions of roughly 50 base pairs [28]. The key histones participating in the assembly of a nucleosome include histones H2A, H2B, H3 and H4. These histones form hetero-dimers resulting in each being twice represented in the nucleosomal unit [29-31]. Structurally, histones are highly conserved, including a folded core followed by an unstructured tail [30, 31]. A globular domain forms the histone core as a

helix-turn-helix motif, which allows dimerization [31]. In contrast, the tails of histones do not exist in defined conformations except when attached to their cognate proteins [31]. Within the sequence of histone tail domains is a large representation of conserved amino acid residues including lysine, arginine, and serine [31, 32]. Under normal conditions, histone tails have a net basic charge facilitating their interaction with the poly-anionic backbone of DNA, thereby contributing to the stability of nucleosomes [31]. Consequently, chromatin structure and transcriptional regulation are commonly mediated through post-translational modifications that impact specific residues within the sequence of these tails [33, 34]. Modifications to tail residues can regulate the accessibility of nuclear factors to regions of DNA or induce the recruitment of such factors involved in chromatin structural and transcriptional regulatory pathways [33, 34].

The Histone-DNA interface is formed principally by inelastic hydrogen bonds between the phosphate oxygen of DNA and the main chain amide of the histone. Electrostatic interactions between basic side chains and negatively charged phosphate groups and other nonpolar interactions further strengthen the association between histones and DNA [35]. While this, in theory, should facilitate the establishment of nucleosomes upon any DNA sequence, there are likely specific sequence parameters for nucleosomal placement [36]. The composition of the DNA sequences, by which the histone core is enveloped, is likely a major factor contributing to the positioning of core histones and the dynamic comportment of the nucleosome under the influence of the SWI/SNF ATPase and sequence-specific transcription factors [37]. The most broadly characterized nucleosomal assembly is the 30 nm fiber [38], which is anchored by linker histones [39-41] and the relative juxtaposition of each nucleosome [42], establishing close physical proximity while generating only marginal internucleosomal attraction energy [38, 43-45]. Hence, this architecture allows a great degree of variation in condensation without producing serious topological changes. Chromatin exists in a series of more densely compacted structures [46], which are commonly driven by interaction with non-histone, structural proteins [47].

In recent decades, a number of process which impact the structure and/or function of chromatin including post-translational modifications of histones, DNA methylation, incorporation of histone variants, and ATP-dependent chromatin remodelling have been the subjects of intense study. The findings of these studies clearly show that chromatin modifications and the complexes involved with their facilitation are linked to the control of many biological processes which depend upon the level of chromatin accessibility [48-51]. Such processes include chromosome segregation during mitosis, X chromosome inactivation, gene expression, DNA repair, and chromatin condensation during apoptosis [23, 52-56].

Chromatin modifications convey epigenetic regulation of protein expression without alterations in DNA sequence. Disturbing the equilibrium of epigenetic networks has been shown to be associated with numerous pathological events, including syndromes involving chromosomal instability, neurological disorders, and tumorigenesis [57-59]. Advances in knowledge related to epigenetic inheritance and chromatin structure/regulation have paved the way for promising novel therapeutics directed against the specific factors that are responsi-

ble [60]. Of particular importance in the role of chromatin modifications in human disease are methylation of DNA, histone targets, and other regulatory targets.

2. DNA methylation in tumorigenesis

Methylation of DNA is a covalent modification that occurs at cytosines within CpG-rich regions of DNA and is catalyzed by DNA methyltransferases [61, 62]. The methylation of DNA affects the binding of proteins to their cognate DNA sequences [61, 63]. Such addition of methyl groups can prevent the binding of basal transcriptional machinery and ubiquitous transcription factors [61]. Thus, DNA methylation contributes to epigenetic inheritance, allele-specific expression, inactivation of the X chromosome, genomic stability and embryonic development. It is through these pathways that progressive DNA methylation is thought to be an agent for both normal aging as well as neoplasias [64, 65]. The majority of methylated CpG islands are located within repetitive elements including centromeric repeats, satellite sequences and gene repeats. These CpG regions are often found at the 5' end of genes where DNA methylation affects transcription by recruiting methyl-CpG binding domain (MBD) proteins that function as adaptors between methylated DNA and chromatin-modifying enzymes [66]. There is a clear relationship between DNA methylation and other silencing mechanisms including histone modifications and chromatin remodeling [65, 66]. In fact, several studies suggest that DNA methylation affects genes that are already suppressed by other mechanisms [65].

Changes in the pattern of DNA methylation have been correlated with altered histone post-translational modifications and genetic lesions [67]. Either hypermethylation or hypomethylation have been identified in almost all types of cancer cells examined, to date [18, 21, 68]. Hypomethylation at centromeric repeat sequences has been linked to genomic instability [18] whereas local hypermethylation of individual genes has been associated with aberrant gene silencing [21]. In oncogenic cells, hypermethylation is often correlated with the repression of tumor suppressor genes while hypomethylation is associated with the activation of genes required for invasion and metastasis [68, 69]. In neoplastic tissues, the incidence of hypermethylation in genes with promoter associated CpG islands is markedly increased which, in turn, is associated with repression of tumor suppressors [70]. Although the complete mechanistic pathway for DNA methylation in cancers is still being determined, aberrant methylation in tumors is already being examined as an instrument for diagnosis [21, 70]. For example, techniques, such as the polymerase chain reaction amplification of bisulfite-modified DNA, have enabled the study of patterns of DNA methylation [71-73]. These methods are currently being improved and adapted for cancer cell identification, profiling of tumor-suppressor-gene expression, and prognostic factors that are linked to CpG island hypermethylation [74]. Likewise, reversal of hypermethylation by several indiscriminant demethylating compounds has been approved for therapeutic intervention associated with blood-borne cancers [21].

Detection of DNA methylation has recently been added to the armory of preventative/diagnostic medicine for the prevention and treatment of colorectal cancer [75]. This represents

the most common form of gastrointestinal cancer and is a leading killer among all malignancies. The colonoscopy is broadly employed for detection of lesions which often give rise to colorectal tumors. The invasiveness of this procedure and consequent lack of patient cooperation with recommended colonoscopies is a limiting factor in the efficacy of this procedure as a preventative. Fortunately, epigenetic screening has arisen as a new tier in preventative medicine targeting colorectal cancer. Specifically, DNA methylation is associated with gene-silencing related to onset of colorectal cancer. Given that these changes are detectable prior to tumorigenesis, target-specific screening of DNA methylation represents a promising front in the war against colorectal cancer [75].

Similar to colorectal cancer, the role of DNA methylation in prostate cancers has been the subject of numerous studies [76-78]. Indeed, aberrant hyper/hypo methylation has been linked in numerous prostate-specific malignant processes ranging from early tumorigenesis to late stage, androgen independent tumors [79]. The identification of specific targets which are down-regulated as a result of hypermethylation at their promoters has led to the development of methylation biomarkers for early detection [80]. These targets of inactivation by promoter hypermethylation include Ras-association domain family 1A (RASSF1A), GSTP1, and retinoic acid receptor beta2 (RARbeta2). Though the role of hypomethylation in prostate cancer is less understood, there are several recent studies which link it to alterations in the expression of genes associated with early and late stage prostate tumors [81-83].

Additional studies indicate that hyper/hypomethylation of specific promoter regions is associated with tumorigenesis in a broad range of tissues including lung, breast, thyroid, head and neck squamous cell carcinomas, and hepatocellular carcinomas [84-86]. There are ongoing studies in dozens of other tissue types indicating a role for hyper/hypomethylation in a broadening range of cancers. Thus, aberrant alterations in methylation promise to provide a broad-spectrum mechanism for early detection and prognostication of tumors.

3. Histone methylation in tumorigenesis

Modifications to histone tails comprise the broadest range of variation in epigenetic controls, encompassing more than four dozen known sites of alteration [87]. Histone proteins are the targets of many forms of post-translational modification such as citrullination, acetylation, phosphorylation, SUMOylation, ADP-ribosylation and methylation (Figure 1) [87, 88]. These alterations are translated into biological consequences by impacting the structure of the nucleosome as well as facilitating the recruitment of specific regulatory complexes. The combination of different histone modifications in concert communicates a "histone code" that is interpreted in the form of distinct nuclear events [89].

Histone methylation has been observed to be a mark that imparts long-term epigenetic memory [90]. Histone lysine methylation is a central factor in such processes as X chromosome inactivation, DNA methylation, transcriptional regulation, and the formation of heterochromatin [91, 92]. This modification, catalyzed by histone methyltransferases, often facilitates the regulation of protein expression in a residue-dependent manner [90]. The de-

degree of achievable specificity is increased by the breadth of biological outcomes which are dependent upon whether a residue is mono-, di-, or tri-methylated [93-95]. Likewise, it has also been widely observed that histone lysine methylation works concomitantly with many transient histone modifications, thereby further enhancing the degree of information which can be communicated by this epigenetic modification [15].

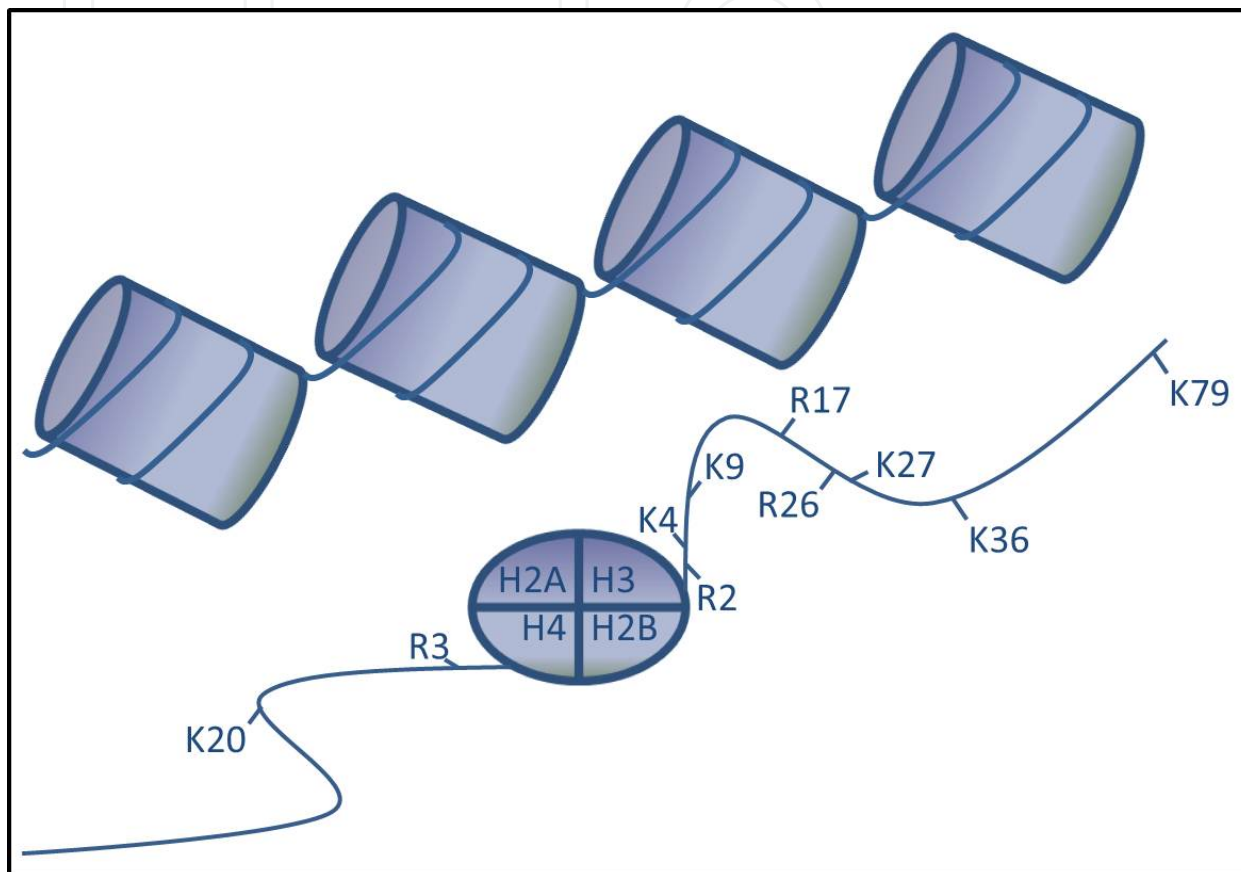


Figure 1. Common sites of Histone Methylation

Almost all histone lysine methyltransferases are dependent upon a SET domain for catalyzing the transfer of methyl groups. The SET domain is present in many proteins that control a range of biological processes, including several involved in development and proper cell cycle progression [7, 96]. Promoter associated, residue-specific histone methylation often correlates with distinct patterns of protein expression [96]. The bulk of known modifications occur on histone H3 which thereby serves as a central conduit of epigenetic regulation. Lysine methylation at histone H3, lysine 9 (H3K9), H3K27, and H4K20 is most often associated with gene silencing, whereas methylation of H3K4, H3K36, or H3K79 is commonly linked to the activation of transcription [7, 96]. Accumulating evidence points to histone methylation in the recruitment of chromatin remodeling complexes, such as CHD1, an ATP-dependent chromatin remodeling factor that binds specifically to methylated the forms of H3K4 [97]. While histone lysine methylation was previously believed to be a permanent mark, a num-

ber of enzymes have now been identified that are capable of reversing histone methylation in a site-specific manner [98-100].

The presence of histone variants creates yet another tier to the potential of epigenetic mechanisms to communicate cellular information [53]. Variants affect the nucleosomal architecture as well as the proclivity of local chromatin to be remodeled. Thus, the inclusion of histone variants may modify nucleosome mobility, stability, and/or potential patterns of histone modifications. These, in turn, impact higher order structure and downstream events [101-104]. For example, a specialized H3-like variant CENP-A, replaces H3 in centromeric nucleosomes to establish a distinct architecture that is essential for proper segregation of the chromosomes [105]. In recent years, there have been an increasing number of experimental outcomes emphasizing the biological relevance of histone variants and their central role in epigenetic control [53].

Regulating the architecture of chromatin involves complex and dynamic mechanisms. The structure of chromatin is controlled on multiple levels by distinct processes such as nucleosome remodeling, DNA methylation, histone post-translational modifications, incorporation of histone variants, and non-coding RNA. Aberrant activity within such epigenetic processes is likely to broadly affect protein expression as well as other biological events such as apoptosis and condensation and segregation of chromosomes.

Tumorigenesis is a graded process through which a succession of genetic aberrations leads to the progressive transformation of healthy cells. While modifications in genetic sequence certainly account for many of these aberrations, an increasing number of modifications in gene expression observed in tumorigenesis have been found to be the result by epigenetic aberrations. These observations point to the relevance of epigenetic mechanisms in the maintenance of proper cell function. Aberrant events related to such mechanisms often act in concert with genetic mutations thereby contributing to the development and progression of cancer.

Over the last two decades, an increasing number of investigations have highlighted the aberrant gain or loss of histone methyltransferase activity in carcinogenesis. At one end of the spectrum, it has been shown that mice which fail to express the H3K9-specific histone methyltransferase, SUV39H1, are subject to increased incidence of chromosomal instability and subsequent tumorigenic potential [106]. At the opposite end of the spectrum, it is over-expression of Smyd3, another histone methyltransferase that is specific for H3K4, that has been shown to be responsible for unrestrained proliferation of many cancer cells [107]. A transcription factor binding element polymorphism in the upstream regulatory sequence for Smyd3 has been associated with an increased risk for cancer [108, 109].

In addition to histone targets, some SET domain-containing methyltransferases have been shown to methylate other proteins including tumor suppressors. Smyd2, which methylates H3K36 [6, 110], has also been directly linked to the regulation of p53 [111, 112]. Methylating lysine 370 of p53, Smyd2 has been shown to inhibit the transcriptional regulatory activity of p53. Smyd2 regulation of the retinoblastoma tumor suppressor (RB) has also been observed by its capacity to methylate of RB at K860 [113]. In a second example, Set9, which methylates

H3K4 [114, 115], has also been linked to the regulation of p53 by its capacity to methylate that protein at lysine 372 [116, 117]. Methylation of that site stabilizes p53 and limits its localization to the nucleus [116].

The broad roles of aberrant lysine methylation in the induction of carcinogenesis have paved the way for a novel line of cancer therapeutics. [118]. Those therapeutics bank on the potential to manipulate of the demethylating activity of a host of demethylases. The fact that many demethylases target highly specific substrates heightens their potential utility as highly effective therapeutics with lower likelihood of instigating adverse effects.

4. Conclusion

While it is true that chromatin architecture has the capacity to be epigenetically maintained and inherited via modified states of methylation, recent studies have highlighted the fact that methylation-induced control of gene expression may be altered by environmental stressors and toxicants. Such modifications may, in consequence, induce aberrations toward genome integrity and stability. Distinct from genetic mutations, these epigenetic aberrations have been termed epimutations. In contrast to genetic mutations, which may be passively inherited, epimutations require active maintenance [119]. That epimutations rare appearance in normal tissues highlights the potential for epigenetic therapies based on high tumor specificity. Likewise, while therapeutics based on genetic deletions commonly induce an irreversible loss of gene function, epigenetic alterations are reversible, further enhancing their potential utility for therapeutic intervention [120]. Reversal of epimutations to restore normal expression of tumor suppressors has become the holy grail in epigenetic cancer therapeutics. Already, numerous studies have proven that aberrant gene silencing mediated by DNA methylation can be easily reversed by the incorporation of DNA methyltransferase inhibitors [121]. Positive results have been observed after treating tumor cells with such pharmacological agents [122, 123].

In the last two decades, our knowledge of chromatin methylation patterns and their role in the regulation of nuclear processes have been broadly elucidated. Understanding those patterns of histone changes, decoding the association between those alterations and DNA methylation, and characterizing their relevance in tumorigenesis comprise the next hurdles in the etiology of the role of methylation in cancer.

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References

- [1] Natoli G: Maintaining Cell Identity through Global Control of Genomic Organization. *Immunity* 2010, 33(1):12-24.
- [2] Müller C, Leutz A: Chromatin remodeling in development and differentiation. *Current Opinion in Genetics & Development* 2001, 11(2):167-174.
- [3] Cavalli G: Chromatin and epigenetics in development: blending cellular memory with cell fate plasticity. *Development* 2006, 133(11):2089-2094.
- [4] Vasanthi D, Mishra RK: Epigenetic regulation of genes during development: A conserved theme from flies to mammals. *Journal of Genetics and Genomics* 2008, 35(7):413-429.
- [5] Kiefer JC: Epigenetics in development. *Developmental Dynamics* 2007, 236(4):1144-1156.
- [6] Brown M, Sims R, Gottlieb P, Tucker P: Identification and characterization of Smyd2: a split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase that interacts with the Sin3 histone deacetylase complex. *Molecular Cancer* 2006, 5(1):26.
- [7] Jenuwein T, Allis CD: Translating the Histone Code. *Science* 2001, 293(5532):1074-1080.
- [8] Jenuwein T: The epigenetic magic of histone lysine methylation. *FEBS Journal* 2006, 273(14):3121-3135.
- [9] Festenstein R, Aragon L: Decoding the epigenetic effects of chromatin. *Genome Biology* 2003, 4(10):342.

- [10] Imhof A: Epigenetic regulators and histone modification. *Briefings in Functional Genomics & Proteomics* 2006, 5(3):222-227.
- [11] Mito Y, Henikoff JG, Henikoff S: Genome-scale profiling of histone H3.3 replacement patterns. *Nat Genet* 2005, 37(10):1090-1097.
- [12] Zhang Y, Fatima N, Dufau ML: Coordinated Changes in DNA Methylation and Histone Modifications Regulate Silencing/Derepression of Luteinizing Hormone Receptor Gene Transcription. *Molecular and Cellular Biology* 2005, 25(18):7929-7939.
- [13] Misteli T: Beyond the Sequence: Cellular Organization of Genome Function. *Cell* 2007, 128(4):787-800.
- [14] Barkess G: Chromatin remodeling and genome stability. *Genome Biology* 2006, 7(6):319.
- [15] Turner BM: Cellular Memory and the Histone Code. *Cell* 2002, 111(3):285-291.
- [16] Turner BM: Reading signals on the nucleosome with a new nomenclature for modified histones. *Nat Struct Mol Biol* 2005, 12(2):110-112.
- [17] Staub E, Grone J, Mennerich D, Ropcke S, Klamann I, Hinzmänn B, Castanos-Velez E, Mann B, Pilarsky C, Brummendorf T et al: A genome-wide map of aberrantly expressed chromosomal islands in colorectal cancer. *Molecular Cancer* 2006, 5(1):37.
- [18] Ducasse M, Brown M: Epigenetic aberrations and cancer. *Molecular Cancer* 2006, 5(1):60.
- [19] Ballestar E, Esteller M: Chapter 9 Epigenetic Gene Regulation in Cancer. In: *Advances in Genetics*. Edited by Veronica van H, Robert EH, vol. Volume 61: Academic Press; 2008: 247-267.
- [20] Sandoval J, Esteller M: Cancer epigenomics: beyond genomics. *Current Opinion in Genetics & Development* 2012, 22(1):50-55.
- [21] Shenker N, Flanagan JM: Intragenic DNA methylation: implications of this epigenetic mechanism for cancer research. *Br J Cancer* 2012, 106(2):248-253.
- [22] Baylin SB, Jones PA: A decade of exploring the cancer epigenome — biological and translational implications. *Nat Rev Cancer* 2011, 11(10):726-734.
- [23] Fullgrabe J, Kavanagh E, Joseph B: Histone onco-modifications. *Oncogene* 2011, 30(31):3391-3403.
- [24] Alabert C, Groth A: Chromatin replication and epigenome maintenance. *Nat Rev Mol Cell Biol* 2012, 13(3):153-167.
- [25] Bell O, Tiwari VK, Thomä NH, Schübeler D: Determinants and dynamics of genome accessibility. *Nat Rev Genet* 2011, 12(8):554-564.

- [26] Varga-Weisz PD, Becker PB: Regulation of higher-order chromatin structures by nucleosome-remodelling factors. *Current Opinion in Genetics & Development* 2006, 16(2):151-156.
- [27] Svaren J, Hörz W: Regulation of gene expression by nucleosomes. *Current Opinion in Genetics & Development* 1996, 6(2):164-170.
- [28] Fransz P, de Jong H: From nucleosome to chromosome: a dynamic organization of genetic information. *The Plant Journal* 2011, 66(1):4-17.
- [29] Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ: Crystal structure of the nucleosome core particle at 2.8[thinsp]Å resolution. *Nature* 1997, 389(6648):251-260.
- [30] Richmond TJ, Davey CA: The structure of DNA in the nucleosome core. *Nature* 2003, 423(6936):145-150.
- [31] Luger K: Dynamic nucleosomes. *Chromosome Research* 2006, 14(1):5-16.
- [32] Khorasanizadeh S: The Nucleosome: From Genomic Organization to Genomic Regulation. *Cell* 2004, 116(2):259-272.
- [33] Bassett A, Cooper S, Wu C, Travers A: The folding and unfolding of eukaryotic chromatin. *Current Opinion in Genetics & Development* 2009, 19(2):159-165.
- [34] Vitolo JM, Thiriet C, Hayes JJ: The H3-H4 N-Terminal Tail Domains Are the Primary Mediators of Transcription Factor IIIA Access to 5S DNA within a Nucleosome. *Molecular and Cellular Biology* 2000, 20(6):2167-2175.
- [35] Davey CA, Sargent DF, Luger K, Maeder AW, Richmond TJ: Solvent Mediated Interactions in the Structure of the Nucleosome Core Particle at 1.9Å Resolution. *Journal of Molecular Biology* 2002, 319(5):1097-1113.
- [36] Kaplan N, Moore IK, Fondufe-Mittendorf Y, Gossett AJ, Tillo D, Field Y, LeProust EM, Hughes TR, Lieb JD, Widom J et al: The DNA-encoded nucleosome organization of a eukaryotic genome. *Nature* 2009, 458(7236):362-366.
- [37] Vicent GP, Nacht AS, Smith CL, Peterson CL, Dimitrov S, Beato M: DNA Instructed Displacement of Histones H2A and H2B at an Inducible Promoter. *Molecular Cell* 2004, 16(3):439-452.
- [38] Robinson PJJ, Rhodes D: Structure of the '30nm' chromatin fibre: A key role for the linker histone. *Current Opinion in Structural Biology* 2006, 16(3):336-343.
- [39] Oudet P, Gross-Bellard M, Chambon P: Electron microscopic and biochemical evidence that chromatin structure is a repeating unit. *Cell* 1975, 4(4):281-300.
- [40] Schalch T, Duda S, Sargent DF, Richmond TJ: X-ray structure of a tetranucleosome and its implications for the chromatin fibre. *Nature* 2005, 436(7047):138-141.
- [41] Bharath MMS, Chandra NR, Rao MRS: Molecular modeling of the chromatosome particle. *Nucleic Acids Research* 2003, 31(14):4264-4274.

- [42] Bednar J, Horowitz RA, Grigoryev SA, Carruthers LM, Hansen JC, Koster AJ, Woodcock CL: Nucleosomes, linker DNA, and linker histone form a unique structural motif that directs the higher-order folding and compaction of chromatin. *Proceedings of the National Academy of Sciences* 1998, 95(24):14173-14178.
- [43] Bednar J, Dimitrov S: Chromatin under mechanical stress: from single 30 nm fibers to single nucleosomes. *FEBS Journal* 2011, 278(13):2231-2243.
- [44] Cui Y, Bustamante C: Pulling a single chromatin fiber reveals the forces that maintain its higher-order structure. *Proceedings of the National Academy of Sciences* 2000, 97(1):127-132.
- [45] Staynov D, Proykova Y: Topological constraints on the possible structures of the 30 nm chromatin fibre. *Chromosoma* 2008, 117(1):67-76.
- [46] Adkins NL, Watts M, Georgel PT: To the 30-nm chromatin fiber and beyond. *Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression* 2004, 1677(1-3):12-23.
- [47] McBryant S, Adams V, Hansen J: Chromatin architectural proteins. *Chromosome Research* 2006, 14(1):39-51.
- [48] Reiner SL: Epigenetic control in the immune response. *Human Molecular Genetics* 2005, 14(suppl 1):R41-R46.
- [49] Turner BM: Defining an epigenetic code. *Nat Cell Biol* 2007, 9(1):2-6.
- [50] Margueron R, Trojer P, Reinberg D: The key to development: interpreting the histone code? *Current Opinion in Genetics & Development* 2005, 15(2):163-176.
- [51] Lin W, Dent SYR: Functions of histone-modifying enzymes in development. *Current Opinion in Genetics & Development* 2006, 16(2):137-142.
- [52] Martin C, Zhang Y: The diverse functions of histone lysine methylation. *Nat Rev Mol Cell Biol* 2005, 6(11):838-849.
- [53] Bernstein E, Hake SB: The nucleosome: a little variation goes a long way This paper is one of a selection of papers published in this Special Issue, entitled 27th International West Coast Chromatin and Chromosome Conference, and has undergone the Journal's usual peer review process. *Biochemistry and Cell Biology* 2006, 84(4):505-507.
- [54] Barakat TS, Gribnau J: X chromosome inactivation in the cycle of life. *Development* 2012, 139(12):2085-2089.
- [55] Hassa PO, Hottiger MO: An epigenetic code for DNA damage repair pathways? *Biochemistry and Cell Biology* 2005, 83(3):270-285.
- [56] Méndez-Acuña L, Di Tomaso MV, Palitti F, Martínez-López W: Histone Post-Translational Modifications in DNA Damage Response. *Cytogenetic and Genome Research* 2010, 128(1-3):28-36.

- [57] Grønbæk K, Hother C, Jones PA: Epigenetic changes in cancer. *APMIS* 2007, 115(10):1039-1059.
- [58] Fraga MF, Esteller M: Towards the Human Cancer Epigenome: A First Draft of Histone Modifications. *Cell Cycle* 2005, 4(10):1377-1381.
- [59] Agrelo R, Cheng W-H, Setien F, Roper S, Espada J, Fraga MF, Herranz M, Paz MF, Sanchez-Céspedes M, Artiga MJ et al: Epigenetic inactivation of the premature aging Werner syndrome gene in human cancer. *Proceedings of the National Academy of Sciences* 2006, 103(23):8822-8827.
- [60] Popovic R, Licht JD: Emerging Epigenetic Targets and Therapies in Cancer Medicine. *Cancer Discovery* 2012, 2(5):405-413.
- [61] Bogdanović O, Veenstra G: DNA methylation and methyl-CpG binding proteins: developmental requirements and function. *Chromosoma* 2009, 118(5):549-565.
- [62] Klose RJ, Bird AP: Genomic DNA methylation: the mark and its mediators. *Trends in Biochemical Sciences* 2006, 31(2):89-97.
- [63] Wade PA: Methyl CpG-binding proteins and transcriptional repression*. *BioEssays* 2001, 23(12):1131-1137.
- [64] Vaissière T, Sawan C, Herceg Z: Epigenetic interplay between histone modifications and DNA methylation in gene silencing. *Mutation Research/Reviews in Mutation Research* 2008, 659(1-2):40-48.
- [65] Kanwal R, Gupta S: Epigenetic modifications in cancer. *Clinical Genetics* 2012, 81(4):303-311.
- [66] Hendrich B, Tweedie S: The methyl-CpG binding domain and the evolving role of DNA methylation in animals. *Trends in Genetics* 2003, 19(5):269-277.
- [67] Jones PA, Baylin SB: The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 2002, 3(6):415-428.
- [68] Tryndyak V, Kovalchuk O, Pogribny IP: Identification of differentially methylated sites within unmethylated DNA domains in normal and cancer cells. *Analytical Biochemistry* 2006, 356(2):202-207.
- [69] Tryndyak VP, Kovalchuk O, Pogribny IP: Loss of DNA methylation and histone H4 lysine 20 trimethylation in human breast cancer cells is associated with aberrant expression of DNA methyltransferase 1, Suv4-20h2 histone methyltransferase and methyl-binding proteins. *Cancer Biology & Therapy* 2006, 5(1):65-70.
- [70] Jones PA, Baylin SB: The Epigenomics of Cancer. *Cell* 2007, 128(4):683-692.
- [71] Baylin SB, Herman JG: DNA hypermethylation in tumorigenesis: epigenetics joins genetics. *Trends in Genetics* 2000, 16(4):168-174.

- [72] Lyko F, Stach D, Brenner A, Stilgenbauer S, Döhner H, Wirtz M, Wiessler M, Schmitz OJ: Quantitative analysis of DNA methylation in chronic lymphocytic leukemia patients. *ELECTROPHORESIS* 2004, 25(10-11):1530-1535.
- [73] Teodoridis JM, Strathdee G, Brown R: Epigenetic silencing mediated by CpG island methylation: potential as a therapeutic target and as a biomarker. *Drug Resistance Updates* 2004, 7(4-5):267-278.
- [74] Omenn GS: Strategies for plasma proteomic profiling of cancers. *PROTEOMICS* 2006, 6(20):5662-5673.
- [75] Patai ÁV, Molnár B, Kalmár A, Schöller A, Tóth K, Tulassay Z: Role of DNA Methylation in Colorectal Carcinogenesis. *Digestive Diseases* 2012, 30(3):310-315.
- [76] Meiers I, Shanks JH, Bostwick DG: Glutathione S-transferase pi (GSTP1) hypermethylation in prostate cancer: review 2007. *Pathology - Journal of the RCPA* 2007, 39(3):299-304 210.1080/00313020701329906.
- [77] Yamanaka M, Watanabe M, Yamada Y, Takagi A, Murata T, Takahashi H, Suzuki H, Ito H, Tsukino H, Katoh T et al: Altered methylation of multiple genes in carcinogenesis of the prostate. *International Journal of Cancer* 2003, 106(3):382-387.
- [78] Brooks JD, Weinstein M, Lin X, Sun Y, Pin SS, Bova GS, Epstein JI, Isaacs WB, Nelson WG: CG island methylation changes near the GSTP1 gene in prostatic intraepithelial neoplasia. *Cancer Epidemiology Biomarkers & Prevention* 1998, 7(6):531-536.
- [79] Wolff DW, Xie Y, Deng C, Gatalica Z, Yang M, Wang B, Wang J, Lin M-F, Abel PW, Tu Y: Epigenetic repression of regulator of G-protein signaling 2 promotes androgen-independent prostate cancer cell growth. *International Journal of Cancer* 2012, 130(7):1521-1531.
- [80] Nakayama M, Gonzalgo ML, Yegnasubramanian S, Lin X, De Marzo AM, Nelson WG: GSTP1 CpG island hypermethylation as a molecular biomarker for prostate cancer. *Journal of Cellular Biochemistry* 2004, 91(3):540-552.
- [81] Cho NY, Kim BH, Choi M, Yoo EJ, Moon KC, Cho YM, Kim D, Kang GH: Hypermethylation of CpG island loci and hypomethylation of LINE-1 and Alu repeats in prostate adenocarcinoma and their relationship to clinicopathological features. *The Journal of Pathology* 2007, 211(3):269-277.
- [82] Cho N-Y, Kim J, Moon K, Kang G: Genomic hypomethylation and CpG island hypermethylation in prostatic intraepithelial neoplasm. *Virchows Archiv* 2009, 454(1):17-23.
- [83] Ogishima T, Shiina H, Breault JE, Tabatabai L, Bassett WW, Enokida H, Li L-C, Kawakami T, Urakami S, Ribeiro-Filho LA et al: Increased Heparanase Expression Is Caused by Promoter Hypomethylation and Up-Regulation of Transcriptional Factor Early Growth Response-1 in Human Prostate Cancer. *Clinical Cancer Research* 2005, 11(3):1028-1036.

- [84] Hansen KD, Timp W, Bravo HC, Sabunciyan S, Langmead B, McDonald OG, Wen B, Wu H, Liu Y, Diep D et al: Increased methylation variation in epigenetic domains across cancer types. *Nat Genet* 2011, 43(8):768-775.
- [85] Shames DS, Girard L, Gao B, Sato M, Lewis CM, Shivapurkar N, Jiang A, Perou CM, Kim YH, Pollack JR et al: A Genome-Wide Screen for Promoter Methylation in Lung Cancer Identifies Novel Methylation Markers for Multiple Malignancies. *PLoS Med* 2006, 3(12):e486.
- [86] Colacino JA, Arthur AE, Dolinoy DC, Sartor MA, Duffy SA, Chepeha DB, Bradford CR, Walline HM, McHugh JB, D'Silva N et al: Pretreatment dietary intake is associated with tumor suppressor DNA methylation in head and neck squamous cell carcinomas. *Epigenetics* 2012, 7(8):4-12.
- [87] Lee J-S, Smith E, Shilatifard A: The Language of Histone Crosstalk. *Cell* 2010, 142(5):682-685.
- [88] Hayes JJ, Clark DJ, Wolffe AP: Histone contributions to the structure of DNA in the nucleosome. *Proceedings of the National Academy of Sciences* 1991, 88(15):6829-6833.
- [89] Strahl BD, Allis CD: The language of covalent histone modifications. *Nature* 2000, 403(6765):41-45.
- [90] Greer EL, Shi Y: Histone methylation: a dynamic mark in health, disease and inheritance. *Nat Rev Genet* 2012, 13(5):343-357.
- [91] Lachner M, Jenuwein T: The many faces of histone lysine methylation. *Current Opinion in Cell Biology* 2002, 14(3):286-298.
- [92] Kouzarides T: Histone methylation in transcriptional control. *Current Opinion in Genetics & Development* 2002, 12(2):198-209.
- [93] Wang H, An W, Cao R, Xia L, Erdjument-Bromage H, Chatton B, Tempst P, Roeder RG, Zhang Y: mAM Facilitates Conversion by ESET of Dimethyl to Trimethyl Lysine 9 of Histone H3 to Cause Transcriptional Repression. *Molecular Cell* 2003, 12(2):475-487.
- [94] Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein BE, Emre NCT, Schreiber SL, Mellor J, Kouzarides T: Active genes are tri-methylated at K4 of histone H3. *Nature* 2002, 419(6905):407-411.
- [95] Khorasanizadeh S: Recognition of methylated histones: new twists and variations. *Current Opinion in Structural Biology* 2011, 21(6):744-749.
- [96] Sims Iii RJ, Nishioka K, Reinberg D: Histone lysine methylation: a signature for chromatin function. *Trends in Genetics* 2003, 19(11):629-639.
- [97] Sims RJ, Chen C-F, Santos-Rosa H, Kouzarides T, Patel SS, Reinberg D: Human but Not Yeast CHD1 Binds Directly and Selectively to Histone H3 Methylated at Lysine 4

via Its Tandem Chromodomains. *Journal of Biological Chemistry* 2005, 280(51):41789-41792.

- [98] Verrier L, Vandromme M, Trouche D: Histone demethylases in chromatin cross-talks. *Biology of the Cell* 2011, 103(8):381-401.
- [99] Tsukada Y-i, Fang J, Erdjument-Bromage H, Warren ME, Borchers CH, Tempst P, Zhang Y: Histone demethylation by a family of JmjC domain-containing proteins. *Nature* 2006, 439(7078):811-816.
- [100] Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, Casero RA, Shi Y: Histone Demethylation Mediated by the Nuclear Amine Oxidase Homolog LSD1. *Cell* 2004, 119(7):941-953.
- [101] Ahmad K, Henikoff S: The Histone Variant H3.3 Marks Active Chromatin by Replication-Independent Nucleosome Assembly. *Molecular Cell* 2002, 9(6):1191-1200.
- [102] Meneghini MD, Wu M, Madhani HD: Conserved Histone Variant H2A.Z Protects Euchromatin from the Ectopic Spread of Silent Heterochromatin. *Cell* 2003, 112(5):725-736.
- [103] Chakravarthy S, Gundimella SKY, Caron C, Perche P-Y, Pehrson JR, Khochbin S, Luger K: Structural Characterization of the Histone Variant macroH2A. *Molecular and Cellular Biology* 2005, 25(17):7616-7624.
- [104] Ausió J: Histone variants—the structure behind the function. *Briefings in Functional Genomics & Proteomics* 2006, 5(3):228-243.
- [105] Régnier V, Vagnarelli P, Fukagawa T, Zerjal T, Burns E, Trouche D, Earnshaw W, Brown W: CENP-A Is Required for Accurate Chromosome Segregation and Sustained Kinetochore Association of BubR1. *Molecular and Cellular Biology* 2005, 25(10):3967-3981.
- [106] Peters AHFM, O'Carroll D, Scherthan H, Mechtler K, Sauer S, Schöfer C, Weipoltschammer K, Pagani M, Lachner M, Kohlmaier A et al: Loss of the Suv39h Histone Methyltransferases Impairs Mammalian Heterochromatin and Genome Stability. *Cell* 2001, 107(3):323-337.
- [107] Hamamoto R, Furukawa Y, Morita M, Iimura Y, Silva FP, Li M, Yagyu R, Nakamura Y: SMYD3 encodes a histone methyltransferase involved in the proliferation of cancer cells. *Nat Cell Biol* 2004, 6(8):731-740.
- [108] Tsuge M, Hamamoto R, Silva FP, Ohnishi Y, Chayama K, Kamatani N, Furukawa Y, Nakamura Y: A variable number of tandem repeats polymorphism in an E2F-1 binding element in the 5[prime] flanking region of SMYD3 is a risk factor for human cancers. *Nat Genet* 2005, 37(10):1104-1107.
- [109] Frank B, Hemminki K, Wappenschmidt B, Klaes R, Meindl A, Schmutzler RK, Bugert P, Untch M, Bartram CR, Burwinkel B: Variable number of tandem repeats polymor-

- phism in the SMYD3 promoter region and the risk of familial breast cancer. *International Journal of Cancer* 2006, 118(11):2917-2918.
- [110] Diehl F, Brown MA, van Amerongen MJ, Novoyatleva T, Wietelmann A, Harriss J, Ferrazzi F, Böttger T, Harvey RP, Tucker PW et al: Cardiac Deletion of Smyd2 Is Dispensable for Mouse Heart Development. *PLoS ONE* 2010, 5(3):e9748.
 - [111] Wang L, Li L, Zhang H, Luo X, Dai J, Zhou S, Gu J, Zhu J, Atadja P, Lu C et al: Structure of Human SMYD2 Protein Reveals the Basis of p53 Tumor Suppressor Methylation. *Journal of Biological Chemistry* 2011, 286(44):38725-38737.
 - [112] Huang J, Perez-Burgos L, Placek BJ, Sengupta R, Richter M, Dorsey JA, Kubicek S, Opravil S, Jenuwein T, Berger SL: Repression of p53 activity by Smyd2-mediated methylation. *Nature* 2006, 444(7119):629-632.
 - [113] Saddic LA, West LE, Aslanian A, Yates JR, Rubin SM, Gozani O, Sage J: Methylation of the Retinoblastoma Tumor Suppressor by SMYD2. *Journal of Biological Chemistry* 2010, 285(48):37733-37740.
 - [114] Wang H, Cao R, Xia L, Erdjument-Bromage H, Borchers C, Tempst P, Zhang Y: Purification and Functional Characterization of a Histone H3-Lysine 4-Specific Methyltransferase. *Molecular Cell* 2001, 8(6):1207-1217.
 - [115] Kouskouti A, Scheer E, Staub A, Tora L, Talianidis I: Gene-Specific Modulation of TAF10 Function by SET9-Mediated Methylation. *Molecular Cell* 2004, 14(2):175-182.
 - [116] Chuikov S, Kurash JK, Wilson JR, Xiao B, Justin N, Ivanov GS, McKinney K, Tempst P, Prives C, Gamblin SJ et al: Regulation of p53 activity through lysine methylation. *Nature* 2004, 432(7015):353-360.
 - [117] Yoshida K, Miki Y: The cell death machinery governed by the p53 tumor suppressor in response to DNA damage. *Cancer Science* 2010, 101(4):831-835.
 - [118] He Y, Korboukh I, Jin J, Huang J: Targeting protein lysine methylation and demethylation in cancers. *Acta Biochimica et Biophysica Sinica* 2012, 44(1):70-79.
 - [119] Jiang Y-h, Bressler J, Beaudet AL: EPIGENETICS AND HUMAN DISEASE. *Annual Review of Genomics and Human Genetics* 2004, 5(1):479-510.
 - [120] Brown R, Strathdee G: Epigenomics and epigenetic therapy of cancer. *Trends in Molecular Medicine* 2002, 8(4):S43-S48.
 - [121] Lyko F, Brown R: DNA Methyltransferase Inhibitors and the Development of Epigenetic Cancer Therapies. *Journal of the National Cancer Institute* 2005, 97(20):1498-1506.
 - [122] Lind G, Thorstensen L, Lovig T, Meling G, Hamelin R, Rognum T, Esteller M, Lothe R: A CpG island hypermethylation profile of primary colorectal carcinomas and colon cancer cell lines. *Molecular Cancer* 2004, 3(1):28.

- [123] Claus R, Fliegauf M, Stock M, Duque JA, Kolanczyk M, Lübbert M: Inhibitors of DNA methylation and histone deacetylation independently relieve AML1/ETO-mediated lysozyme repression. *Journal of Leukocyte Biology* 2006, 80(6):1462-1472.

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