HHS Public Access

Author manuscript

Curr Protein Pept Sci. Author manuscript; available in PMC 2016 July 05.

Published in final edited form as:

Curr Protein Pept Sci. 2016 ; 17(5): 401–410.

An Overview of Chromatin-Regulating Proteins in Cells

Pingyu Zhang[1,*], **Keila Torres**[2], **Xiuping Liu**[3], **Chang-gong Liu**[3], and **Raphael E. Pollock**[4]

[1]Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

[2]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

[3]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

[4]Department of Surgical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio 43210, USA

Abstract

In eukaryotic cells, gene expressions on chromosome DNA are orchestrated by a dynamic chromosome structure state that is largely controlled by chromatin-regulating proteins, which regulate chromatin structures, release DNA from the nucleosome, and activate or suppress gene expression by modifying nucleosome histones or mobilizing DNA-histone structure. The two classes of chromatin- regulating proteins are 1) enzymes that modify histones through methylation, acetylation, phosphorylation, adenosine diphosphate–ribosylation, glycosylation, sumoylation, or ubiquitylation and 2) enzymes that remodel DNA-histone structure with energy from ATP hydrolysis. Chromatin-regulating proteins, which modulate DNA-histone interaction, change chromatin conformation, and increase or decrease the binding of functional DNA-regulating protein complexes, have major functions in nuclear processes, including gene transcription and DNA replication, repair, and recombination. This review provides a general overview of chromatin-regulating proteins, including their classification, molecular functions, and interactions with the nucleosome in eukaryotic cells.

Keywords

Chromosome; histone; histone modification; chromatin-regulating protein; gene transcription; DNA replication; DNA repair; DNA recombination

Introduction

In human cells, genomic DNA, whose length (2 m) is much greater than the diameter of the nucleus (approximately 3-10 μm), must be highly compacted to fit into the nuclear

[*]Address correspondence to this author at the Department of Gastroenterology, Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA, Tel: 713-792-8399; Fax: 713-792-5572; pinzhang@mdanderson.org and pingyu_zhang@yahoo.com.

Conflict of Interest: The author(s) confirm that this article content has no conflicts of interest.

compartment. Therefore, the DNA in human cells is packaged into chromatin. The basic unit of DNA packaging in chromatin is the nucleosome, a structure that comprises 147 bp of double-strand DNA tightly wrapped around an octamer of histone protein cores. Each histone octamer consists of two copies each of the histones H3, H4, H2A, and H2B. The wrapped DNA contacts the histone octamer at 14 different sites at intervals of approximately 10 bp, and each contact site harbors several different types of noncovalent interactions between the histones and DNA. However, genomic DNA also has to be accessed by protein complexes for gene transcription, DNA replication and DNA repair. The state of chromatin has to be dynamic, switching between a DNA-packaging status, in which the nucleosomes are highly compacted so they can be stored in the comparatively tiny nucleus, and a DNA-unpacking status, in which the nucleosomes are loosened to allow the protein complexes necessary for the molecular processes that use DNA as a template. For example, nucleosomes can loosen to allow the deposition of new histone octamers following DNA replication or to allow the unpacking of cis DNA elements, such as promoters, so they are accessible to DNA-binding transcription factors and/or RNA transcription complexes.

The main factors that determine whether chromatin is in a DNA-packaging or -unpacking state are chromatin-regulating proteins, also known as chromatin regulators. The two classes of chromatin regulators are 1) histone-modifying enzymes and 2) chromatin-remodeling enzymes. Chromatin regulators modulate various DNA-templated processes, such as DNA replication, DNA recombination, gene transcription, DNA damage repair. Dysfunction of the chromatin regulators in human cells results in various human developmental defects and diseases. For human malignancies, genetic alterations or aberrant expression of chromatin regulators have been identified as oncogenic drivers for numerous types of cancer.

Histone Modification

The nucleosome, the basic unit of chromatin, is a DNA-protein structure in which negatively charged genomic DNA is tightly attached around a positively charged octamer of histone proteins. High-resolution X-ray studies of the nucleosome structure have shown that the basic histone N-terminal tails extend from the double strand DNA and contact adjacent histone N-terminal tails. Histone-modifying enzymes covalently modify the N-terminal tails of histone proteins. Modifications that change the positive charge of histones may disrupt the electrostatic interaction between DNA and the histone octamer, thereby interfering with the nucleosome structure. In this way, DNA can be detached from the histone complex and accessed by other proteins such as transcription factors or DNA repair machinery.

The first histone modification to be reported was histone acetylation, in 1964 [1]. Since then, more than 100 different histone post-translational modifications (PTMs) have been identified. Currently, seven major PTMs are known to occur on histone tails in cells: 1) acetylation, 2) methylation, 3) phosphorylation, 4) adenosine diphosphate (ADP)-ribosylation, 5) glycosylation, 6) sumoylation, and 7) ubiquitylation. Each has a distinct function and regulatory mechanism.

Histone Acetylation

Histone acetylation was the first histone PTM discovered [1]. All four core histones in the nucleosome octamer can be acetylated at various lysine residues, such as Lys5 of H2A, Lys5/12/15/20 of H2B, Lys4/9/14/18/23/36/56 of H3, and Lys5/8/12/16 of H4 [2]. Histone acetylation neutralizes the positive charge of the histone core, reducing the binding of histone to negatively charged DNA and leading to the release of DNA to DNA-binding proteins [2]. Therefore, histone acetylation promotes DNA processes that require DNA access, such as gene transcription, DNA replication, and DNA double-strand break (DSB) repair. The accumulation of histone acetylation at multiple lysines has a greater effect on nucleosome structure destabilization than the acetylation at a specific lysine does [3].

The status of histone acetylation on nucleosomes is very dynamic and is regulated by two groups of enzymes that have opposite functions: 1) histone acetyl-transferases (HATs), which cause histone acetylation, and 2) histone deacetylases (HDACs), which cause histone deacetylation. For histone acetylation, HATs covalently attach an acetyl group to the ε-amino group of a lysine side chain using acetyl coenzyme A as a cofactor [4]. Human cells have five groups of HATs: the HAT1, CBP/p300, GNAT, MYST and other HATs. The HAT1 family members, which are also known as type B HATs, predominantly acetylate cytoplasmic free histones and may be involved in chromatin assembly (Table 1) [5]. The other four HAT families, which are also known as type A HATs, acetylate various lysine sites at the N-terminal tails of histones in the nucleosome; thus, type A HATs regulate both the structure of the nucleosome and proteins' access to nucleosomal DNA (Table 1). HATs acetylate not only the lysines on histone tails but also multiple sites in the globular histone core at the major DNA groove, such as H3K56, which is acetylated by the HAT GCN5 [6]. The acetylation of these sites also affects histone-DNA interaction and chromatin structure [6].

In contrast to HATS, HDACs deacetylate the histone core and restore its positive charge, thereby enhancing histone-DNA interaction and blocking proteins' access to DNA [7]. Thus, most HDACs are transcription repressors. There are four classes of HDACs (classes I, II, III, and IV), but HDACs have low substrate specificity for different sites of histone acetylation. Class I HDAC group has HDAC1, HDAC2, HDAC3, and HDAC8. Class IIa includes HDAC4, HDAC5, HDAC7, and HDAC9, whereas HDAC6 and HDAC10 are grouped as class IIb as they contain two catalytic sites. Sirtuins 1-7 belong to class III HDACs, whereas class IV has only HDAC11 with catalytic domain homologous to both class I and class II HDACs [2]. Different HDACs exist in multiple complexes and have redundant functions of deacetylation [8].

Histone acetylation has been shown to destabilize the core histone octamer itself. For example, the acetylation of histone H4K91 induces nucleosome instability by disassociating H3-H4 tetramers from H2A-H2B dimers [9]. Protein structure studies have shown that histone H4K91 locates at the interface of H3-H4 tetramer–H2A-H2B dimer binding. The H4K91A mutant removes the positive charge of the histone, leading to H2A-H2B deposition and histone-DNA dis-association [9].

Histone Methylation

Histone methylation occurs at lysine as mono-, di-, or tri-methylation and occurs at arginine as monomethylation or symmetrical or asymmetrical dimethylation [10, 11]. In contrast to histone acetylation, histone methylation does not change the electric status of histone proteins. Hence, histone methylation does not directly affect the histone-DNA binding structure but generally interferes with the interaction between chromatin-binding factors and DNA. The functions of histone methylation on chromatin assembly and gene transcription are diverse. For example, H3K4 and H3K36 methylation are associated with transcription activation, whereas H3K9 and H3K27 methylation lead to transcription repression [2].

In cells, histone methylation is regulated by two families of enzymes: histone methyltransferases (HMTs) and histone demethylases (HDMs). For histone methylation, HMTs catalyze the transfer of one, two, or three methyl groups of S-adenosyl-L-methionine to histone lysine (ε-amino group) or arginine (ω-guanidino group) residues [4, 12]. Different HMTs have distinct specificities to histone residues and methylation degrees. For instance, the Polycomb proteins EZH1 (enhancer of zeste homolog 1) and EZH2 only catalyze the methylation of H3K27, whereas EHMT1 (euchromatic histone-lysine N-methyltransferase 1) and EHMT2 are specifically active during the mono- and di-methylation of H3K9 [13, 14]. HMTs can be classified into two groups: lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs). Most KMTs have a conserved catalytic SET domain, which is also found in the Polycomb proteins Su(var)3-9, enhancer of zeste, and trithorax. In human cells, there are more than 50 HKMTs, which can be classified into eight subgroups: SET1, SET2, EZH, SYMD, SUV39, PRDM, other SET domain HKMTs, and Non-SET domain HKMTs (Table 2). Only one KMT, DOT1L, has no SET methyltransferase domain [4, 15, 16]. To date, 9 PRMTs have been identified in human cells and can be categorized as type I, II, or III enzymes or as PRMT9 based on their function of arginine methylation. Type I PRMTs (PRMT1, PRMT2, PRMT3, PRMT4 (also known as CARM1), PRMT6, and PRMT8) form asymmetric dimethylarginines. Type II PRMTs (PRMT5 and PRMT7) form symmetric dimethylarginines. The product of type III PRMTs (PRMT7) is stable monomethylarginine. PRMT9 function has not yet been described [12, 17].

HDMs, which were only recently identified, can be divided into two groups: Jumonji domain–containing HDMs and lysine specific demethylase 1 or 2 [10, 18]. Jumonji domain–containing HDMs demethylate H3K9me3 and H3K36me3 using their Jumonji domain as enzymatic unit [19, 20]. Lysine specific demethylase 1 (LSD1) and 2 LSD1 and LSD2 lack a Jumonji domain but remove the methyl group from H3K4me1/2 or H3K9me3 in different complexes [18]. Like HMTs, HDMs have specific targets and sensitivities to specific methylation degrees.

The regulation of nucleosome structure by histone methylation is mediated by the interaction of methylated histones with other chromosome regulators. Studies have shown that the trimethylation of H3K4 is bound by chromatin remodelers such as ING protein via its PHD domain and CHD1 protein via its tandem chromodomain. The interaction either recruit other chromatin regulators or directly modulate the nucleosome [21, 22].

Histone Phosphorylation

Protein phosphorylation is a critical PTM that regulates protein function in a variety of cellular processes, including signal transduction, protein localization, and metabolism. Protein phosphorylation occurs on serine, threonine, and tyrosine residues, and the phosphorylation status is controlled by kinases, which add a phosphorylate group to the hydroxyl group of the target residues, and by phosphatases, which remove a phosphorylate group from the targets. Histone phosphorylation is also a dynamic process that predominantly occurs on the N-terminal amino acids of histone tails. The phosphorylate group attached to the histone substantially reduces the histone's positive charge, which destabilizes histone-DNA interaction, thereby promoting the DNA access by protein complexes [23, 24]. Histone phosphorylation has been found to release nucleosome structure, open chromosome folding, and recruit DNA binding complexes for transcription and DNA repair [25]. After a DSB occurs, the histone H2A variant H2A.X is phosphorylated at serine 139 by ATM or ATR kinase [26]; the phosphorylated H2A.X brings DNA repair machinery to the DSB and increases the DSB's accessibility [27].

A phosphorylated histone residue can also reduce the binding of the adjacent methylated lysine with its binding protein; for example, the phosphorylation of H3S10 blocks the binding of H3K9me3 with HP1 protein [28, 29]. Histone H3K27 and S28 have also shown similar regulation when phosphorylated [30].

Histone ADP-Ribosylation

Mono- or poly-ADP-ribosylation is a common and reversible PTM for many cellular proteins [31]. During this process, ADP-ribosyltransferases (ARTs) can transfer one ADP-ribose moiety from NAD+ to target residues, which could be lysine, arginine, glutamate, aspartate, cysteine, phosphor-serine, or asparagine [31, 32]. Oppositely, ADP-ribose-protein hydrolases (ARHs) or poly(ADP-ribose) glycohydrolases (PARGs) can remove the ADP-ribose unit by hydrolyzing the bonds between a protein and ADP-ribose or between two ADP-riboses [31]. In the nucleosome, all four core histones and the linker histone H1 can be mono- or poly-ADP-ribosylated, but generally only a small percentage of histones are modified *in vivo* [33]. ADP-ribosylation adds negative charges to histones, thereby promoting the loosening of histone-DNA binding and inducing a loosened chromatin state [34]. Studies have shown that DNA damage induces significant poly-ADP-ribosylation on histones H3, H4, H1, and H2B, indicating that poly-ADP-ribosylation has a function in DNA repair processes [32]. In chromatin regions with active transcription, ADP-ribosylation is also active. However, low levels of ADP-ribosylation are also found in silenced chromatin regions [32].

Based on their enzymatic domain structures, ARTs are classified into two groups: ARTDs (or poly ADP-ribose polymerases), and ARTCs. ARTD proteins have a homologous domain to bacteria diphtheria toxin. ARTC proteins have homology to clostridial C2 and C3 toxin [32]. Because ARTCs are secreted out of the cells, ARTCs are not responsible for ADP-ribosylation in the nucleus. Among the ARTDs, ARTD1 is the most involved in poly-ADP-ribosylation for chromatin remodeling, DNA repair, and gene transcription in cells [32]. Other ARTDs play a minor role in histone modification. Three ARHs and one PARG have

been identified in human. ARH1 specifically hydrolyzes ADP-ribose from arginine, whereas ARH2-3 and PARG cannot catalyze this reaction [32].

Histone Sumoylation and Ubiquitylation

Protein sumoylation and ubiquitylation play critical roles in regulating the degradation, localization, activity, and interaction of proteins. Sumoylation and ubiquitylation are similar PTMs in which small ubiquitin-like molecules (100 or fewer amino acids) or ubiquitins (76 amino acids) are attached to the lysine residues of target proteins by the sequential reactions of three enzymes, the E1-activiting, E2-conjugating, and E3-ligating enzymes [35, 36]. Unlike other PTMs of small chemical groups, sumoylation and ubiquitylation covalently attach large peptides to target residues. Ubiquitylation is a reversible process; ubiquitin can be removed by isopeptidases [35]. Histone ubiquitylation has been found on lysines in H2A and H2B tails. Mono-ubiquitylation of H2AK119 has been shown to inhibit gene transcription by interacting with Polycomb group complexes [37]. DNA DSBs induce H2BK123 ubiquitylation, which recruits DNA repair machinery [38, 39]. Sumoylation, which has been found on all core histones in the nucleosome, possibly inhibits gene transcription by blocking acetylation or ubiquitylation [36, 40]. However, the mechanisms of histone sumoylation's effects on nucleosome dynamics are not clear.

Other Histone Modifications

A few histone modifications that are also involved in the regulation of histone function and chromatin structure have been identified recently. For example, the histones H2A, H2B, and H4 are modified by β-linked N-acetylglucosamine (O-GlcNAc) monosaccharides at their serine and threonine sites [41-43]. O-GlcNAc transferase catalyzes this PTM, known as histone O-GlcNAcylation, whereas β-N-acetylglucosaminidase (O-GlcNAcase) removes the sugar from the histones [41]. Histone O-GlcNAcylation might impact other histone modifications, such as H3K9 acetylation, H3S10 phosphorylation, and H3K27 methylation, and regulate chromatin dynamics [44]. However, the function and mechanism of histone O-GlcNAcylation remain to be elucidated.

Several other kinds of non-typical histone modification are histone deimination, tail clipping, and proline isomerization. In histone deamination, peptidyl arginine deiminase type IV PADI4 converts arginine to citrulline, whereas in histone tail clipping, some residues of the histone N-terminal tail are removed [45-48]. In histone proline isomerization, proline isomerases interconvert the cis and trans conformations of proline's peptide bonds [47].

Chromatin Remodeling

In contrast to histone modifications, which do not require energy, chromatin remodeling is an energy-driven process in which chromatin remodelers use the energy of ATP hydrolysis to change the nucleosome structure [49, 50]. Chromatin remodelers have two types of effects on chromatin dynamics: 1) they package genomic DNA, and incorporate histones into the nucleosome, or 2) release DNA from the histones. After DNA replication, chromatin remodelers pack genomic DNA into nucleosomes. During DNA repair, DNA replication, and gene transcription, chromatin remodelers move or eject histones from nucleosomes.

These molecular processes are accomplished through an orchestrated conformation change that involves the DNA-binding and the translocation domains of chromatin remodelers [49]. All chromatin remodelers share similar DNA-dependent ATPase domains and domains that interact with histone modifications, nucleosomes, and other transcription factors [51].

Chromatin Remodeler Families

Human cells have four chromatin remodeler protein families: the SWI/SNF, ISW1, CHD, and INO80 families.

SWI/SNF (**SWI**tching defective/**S**ucrose **N**on**F**ermenting) chromatin remodelers are composed of 8-14 protein subunits. Although this chromatin remodeler family is involved in the disruption of the interaction between genomic DNA and histones to slide, eject, or insert histones, SWI/SNF chromatin remodelers have no function in packaging or assembling chromatin [51]. On the basis of their different subunits, SWI/SNF complexes are divided into two groups: BAF and PBAF (Table 3). The common subunits of both BAF and PBAF are SNF5/INI1, BAF155, BAF57, BAF60, BAF53, BAF45, actin, and BAF170. Only one catalytic ATPase subunit, either BRG1 or BRM, exists in a given SWI/SNF5 complex. The Subunit ARID1A or ARID1B are specific and mutually exclusive for the BAF complex. The BAF180, BAF200, and BRD7 subunits are specific to the PBAF complex [49].

ISWI (**I**mitation **SWI**tch) chromatin remodelers consist of 2 or 8 subunit proteins with special catalytic domains. Human cells have 8 different ISWI chromatin remodeler complexes, which are b-WICH, WICH, NoRC, RSF, ACF, CHRAC, CERF, and NURF (Table 4) [52, 53]. In the b-WICH, WICH, NoRC, RSF, ACF, and CHRAC complexes, the core ATPase subunit is SNF2H, also known as SMARCA5 (SWI-SNF–related matrix-associated actin-dependent regulator of chromatin A5,) [52, 53]. In the NURF and CERF complexes, SMARCA1 (also known as SNF2L) is the core ATPase. The ISWI chromatin remodelers are involved in regulating nucleosome spacing to either promote chromatin compacting (ACF and CHRAC complexes) or inhibit chromatin assembly (NURF complexes) [54, 55]. They are also involved in DNA repair, gene transcription activation, and repression [53]. For example, the catalytic subunit SNF2H is recruited to DNA breaks by the HDAC SIRT6 and loosens the nucleosome to accommodate DNA repair proteins [56].

CHD (**C**hromodomain, **H**elicase, **D**NA binding) chromatin remodelers can be divided into two groups, CHDs and NuRD (nucleosome remodeling and deacetylases), which have 1 and 10 subunits, respectively. In human cells, the catalytic subunits of CHD chromatin remodelers are CHD1, CHD2, CHD6, CHD7, CHD8, and CHD9, whereas the core ATPase subunits of NuRD chromatin remodelers are Mi-2a/CHD3 and Mi-2b/CHD4 (Table 5) [49, 57]. CHD chromatin remodelers have diverse functions. CHD1 normally moves or ejects the nucleosome from the chromosome to promote gene transcription [57]. However, the Mi-2/NuRD complex, which contains both HDAC1 and HDAC2, functions as an HDAC to suppress gene expression [58].

INO80 (**INO**sitol requiring **80**) chromatin remodelers have three different protein complexes (INO80, SRCAP, and TIP60/p400) that each contain approximate 10 subunits (Table 6) [49].

The core ATPases in these complexes are INO80, SRCAP, and p400, which also have histone acetyltransferase activity [59]. Unlike other ATPases, the ATPase of INO80 chromatin remodelers has a long insertion in the middle of the ATPase domain [59]. INO80 chromatin remodelers are involved in promoting gene transcription, DNA repair, and nucleosome restructure [59]. The TIP60/p400 complex is recruited to DNA DSBs and then marks the DNA damage sites by acetylating histones [60-63]. The p400 subunit subsequently loosens the nucleosome's structure to allow DNA repair machinery to access the DNA [62]. The SRCAP complex specifically regulates the replacement of the canonical histone H2A by the histone variant H2A.Z in H2A-H2B dimers during DNA damage response [61].

Chromatin Remodeler Functions

The mechanism by which chromatin remodelers slide DNA around the nucleosome is not quite clear. Current studies support a model in which the DNA binding domain and translocation domain of chromatin remodelers concertedly change their conformation and move DNA to form a loose loop around the nucleosome. The ATPase domains of chromatin remodelers share high homology with known DNA translocases and have been proven to function in DNA translocation events [64]. In this way, chromatin remodelers disrupt DNA–histone interaction, and the histone octamer can be ejected, replaced, or restructured [64]. Chromatin remodelers are involved in DNA repair, replication, transcription, and recombination and in chromosome assembly. On the basis of their interaction with chromatin, chromatin remodelers can be classified as having one of two functions: 1) evicting or replacing histones to open chromatin to DNA or 2) inserting or spacing histones to restructure or assemble chromatin.

Evicting or replacing histones to open chromatin to DNA—Histone ejection and replacement is required for DNA repair, transcription, and replication, and numerous chromatin remodelers play important roles in these DNA processes. For example, INO80 remodelers have been shown to be recruited to DNA DSBs by H2A.XS139 phosphorylation, which is the earliest sign of DNA lesion in mammalian cells [65, 66]. INO80 also forms a functional complex with the transcription factor Yin Yang-1 (YY-1) to accomplish DNA nonhomologous end joining [67]. The ISWI remodeler SNF2H is similarly involved in DNA repair processes. When DNA lesions happen, H3K4 methylation induces the binding of SNF2H to DSBs, and then SNF2H promotes the formation of the DNA repair complex, which contains replication protein A, Rad51, and breast cancer 1, at DSBs [56, 68, 69]. In DNA replication, both SNF2H and INO80 remove the histone and disrupt nucleosomes around the DNA replication fork to promote replication [70, 71]. Chromatin remodelers activate gene transcription by helping recruit the transcription faction, initiate transcription, or elongate transcription. INO80 also activates YY-1 target gene transcription in human cells by facilitating YY-1's access to its target promoters [72]. The human SWI/SNF remodeler is necessary for Tat-dependent mRNA elongation of the HIV promoter [73]. Studies have shown that during active gene transcription, human CHD1 binds to the proximal promoter region, evicts nucleosomes downstream of the promoter, and promotes RNA polymerase II–directed transcription [74].

Inserting or spacing histones to restructure or assemble chromatin—

Replication-dependent chromosome assembly requires the regular deposition of histone core octamers to build nucleosomes. The human ISWI chromatin remodeling complexes CHRAC and ACF are required for the deposition and spacing of histone octamers for chromosome assembly [75]. Recent studies have shown that monomeric ISWI modulates nucleosome repositioning through its ATP-domain during chromosome structure reorganization [76]. Human ACF and NuRD not only contribute to nucleosome positioning over long DNA sequences at the interleukin-2 receptor α locus but also mediate histone deacetylation and interleukin-2 receptor α gene repression by binding to special AT-rich sequence-binding protein 1 [77]. The chromatin remodeler CHD8 interacts with the chromatin insulator protein CTCF to regulate chromatin insulation at the H19–insulin-like growth factor 2 imprinting control region locus [78]. Studies have shown that the human chromatin remodeler SNF2H is required for the cohesion complex's binding to nucleosome DNA to properly segregate chromosomes [79].

Histone Modification–Chromatin Remodeler Interaction

Histone modification and chromatin remodelers have crucial functions in regulating chromatin status, gene activity, and genome stability in the cells. However, these two mechanisms do not work separately; increasing evidence indicate that they interact with each other to regulate chromatin [80].

Interaction of Chromatin Remodelers and Histone Modification

Some chromatin-remodeling proteins have specific domains that recognize and bind to specific histone modifications to function. For example, the bromodomain of SWI/SNF family remodelers has the function of acetylated lysine recognition on histone [80]. Human BRG1, a SWI/SNF ATPase subunit, is recruited by H4K8 and H4K12 acetylation to the interferon-β gene promoter for interferon-β gene transcription activation [81]. In addition, DNA DSB– induced histone H3 acetylation assists in the binding of γ-H2AX with the SWI/SNF complex, which promotes DNA repair processes [82, 83]. Chromatin remodelers have two subdomains, chromodomain and PHD, that can bind to methylated lysines in histone tails [84]. Chromodomains are present in CHD family remodelers. Human CHD1 recognizes the di- and tri-methylation of H3K4 through its two chromodomains and induces gene transcription [85, 86]. ISWI family remodeling enzymes harbor a PHD domain, which interacts with H3K4me3. The ISWI-containing human NURF complex, through the PHD finger of its subunit, bromodomain PHD finger transcription factor, targets H3K4me3 to assist in gene transcription [87]. In some cases, specific histone modifications affect the function of chromatin remodelers. Studies have shown that the acetylation of H4K16 blocks the ISWI chromatin-remodeler's function on nucleosome movement and chromatin assembly [88].

Chromatin Remodelers That Have Histone Modification Activities

Some chromatin remodelers have subunits that directly modify histones to modulate specific histone modifications. For example, Tip60 is an INO80 family remodeling enzyme that has both histone (H4 and H2A) acetyltransferase activity and ATP-dependent H2A.X deposition

activity [89]. In addition, the NuRD remodeler complex, a member of the CHD family, includes two HDAC subunits, HDAC1 and HDAC2, that enables the complex to repress gene transcription through either ATP-dependent nucleosome position or histone deacetylation functions [90, 91].

Conclusion

Since histone modification was first discovered in the 1960s, mounting evidence has illustrated the delicate and complicated mechanisms by which histone modification and chromatin remodelers regulate chromosome structure, gene regulation, DNA replication, and DNA damage response in the cell. These molecular mechanisms are clearly important for many cell functions, such as the cell cycle, cell differentiation, and stem cell maintenance; however, we still have an incomplete understanding of the biology of chromatin-regulating proteins. Additional information is necessary to fully understand their functions in physiologic or pathologic conditions, and develop targeted therapies to combat human diseases with malfunctioning chromatin-regulating proteins.

Acknowledgments

Funding for this research was provided in part by NIH/NCI K08CA160443 (supporting K.T.) and Friends of Sarcoma Funds (supporting P.Z.).

This work is supported by supported by the National Cancer Institute of the National Institutes of Health under Award Number U54CA168512. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We apologize that not all the works in this topic are covered here due to space limits.

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Table 1

Classification of histone acetytransferases.

Subfamily	Histone Acetytransferases				
	GNAT	**MYST**	**p300/CBP**	**HAT1**	**Others**
	GCN5	Tip60	p300	HAT1	ATF-2
	PCAF	MOZ	CBP		SRC1
		MORF			TAFII250
		MOF			
		HBO1			

Table 2

Classfication of histone lysine methyltransferases.

Subfamily	Histone Lysine Methyltransferases							
	SET1	**SET2**	**EZH**	**SYMD**	**SUV39**	**PRDM**	**Other SET**	**Non-SET**
	MLL	NSD1	EZH1	SYMD1	SETMAR	PRDM1	SUV420H1	DOT1L
	MLL2	NSD2	EZH2	SYMD2	SETDB1	PRDM2	SUV420H2	
	MLL3	NSD3		SYMD3	SETDB2	PRDM4	MLL5	
	MLL4	ASH1L		SYMD4	EHMT1	PRDM5	SETD3	
	SET1	SETD2		SYMD5	EHMT2	PRDM6	SETD4	
	SET1L	SET2L			SUV39H1	PRDM7	SETD5	
					SUV39H2	PRDM8	SETD6	
						PRDM9	SETD7	
						PRDM10	SETD8	
						PRDM11		
						PRDM12		
						PRDM13		
						PRDM14		
						PRDM15		
						PRDM16		

Table 3

ATPase and other subunits in BAF and PBAF complexes of SWI/SNF chromatin remodelers.

Complex	SWI/SNF	
	BAF	**PBAF**
ATPase	BRG1/BRM	BRG1
	ARIDA/B	ARID2
	INI1	INI1
	BAF45 A/B/C/D	BAF45 A/B/C/D
	BAF53 A/B	BAF53 A/B
	BAF57	BAF57
	BAF60 A/B/C	BAF60 A/B/C
	BAF155	BAF155
	BAF170	BAF170
	Actin	Actin
	SS18	BAF180
		BRD7

Table 4

ATPase and other subunits in ISWI family chromatin remodeling complexes.

Complex	ISWI							
	ACF	**RSF**	**CERF**	**CHRAC**	**NURF**	**NoRC**	**WICH**	**b-WICH**
ATPase	SNF2H	SNF2H/L	SNF2H/L	SNF2H	SNF2L	SNF2H	SNF2H	SNF2H
	ACF1	RSF1	CECR2	ACF1	BPTF	TIP5	WSTF	WSTF
				CHRAC15	RBAP46/48			DEK
				CHRAC17				CSB
								NM1
								SAP155
								MYBBP1A
								RHII/Gua

Table 5

ATPase and other subunits of CHD family chromatin remodeling complexes.

Complex	CHD		
	NuRD	**NuRD-like**	**CHD**
ATPase	CHD3/4	CHD5	CHD1/2/6/7/8/9
	HDAC1	HDAC2	
	HDAC2	GATAD2 B	
	MTA1/2/3	MTA3	
	RBAP46/48	RBAP46	
	GATAD2 A/B		
	MBD2/3		

Table 6

ATPase and other subunits of INO80 family chromatin remodeling complexes.

Complex	INO80		
	INO80	**Tip60/p400**	**SRCAP**
ATPase	INO80	p400	SRCAP
	RUVBL1/2	RUVBL1/2	RUVBL1/2
	MCRS1	TRRAP	GAS41
	AMIDA	Tip60	BAF53
	BAF53A	BRD8	DMAP1
	YY1	BAF53	YL-1
	IES6	EPC1/2	ARP6
	IES2	YL-1	ZnF-HIT1
	UCH37	GAS41	
	NFRKB	DMAP1	
	INO80E	ING3	
		FLJ11730	
		MRG15	
		MRGX	
		MRGBP	