Chromatin dynamics: Interplay between remodeling enzymes and histone modifications

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Abstract

Chromatin dynamics play an essential role in regulating the accessibility of genomic DNA for a variety of nuclear processes, including gene transcription and DNA repair. The posttranslational modification of the core histones and the action of ATP-dependent chromatin remodeling enzymes represent two primary mechanisms by which chromatin dynamics are controlled and linked to nuclear events. Although there are examples in which a histone modification or a remodeling enzyme may be sufficient to drive a chromatin transition, these mechanisms typically work in concert to integrate regulatory inputs, leading to a coordinated alteration in chromatin structure and function. Indeed, site-specific histone modifications can facilitate the recruitment of chromatin remodeling enzymes to particular genomic regions, or they can regulate the efficiency or the outcome of a chromatin remodeling reaction. Conversely, chromatin remodeling enzymes can also influence, and sometimes directly modulate, the modification state of histones. These functional interactions are generally complex, frequently transient, and often require the association of myriad additional factors.

Keywords

Chromatin remodeling; histone modifications; chromatin dynamics

1. A chromatin primer

Eukaryotic cells organize their genetic material into a DNA-protein complex, called chromatin. In general, chromatin assembly limits the accessibility of genomic sequences, and thus it creates inherent barriers for nuclear events such as transcription, DNA replication, and DNA repair. Consequently, chromatin structure must be dynamic or fluid, and local changes in chromatin structure are utilized to provide the cell with profoundly effective methods for fine-tuning DNA metabolism. Not too surprisingly, disruption of

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mechanisms that control chromatin dynamics can lead to aberrant gene expression, improper or nonexistent DNA repair, chromosomal translocations, inappropriate proliferation, developmental errors, onocogenesis, or even cell death.[1]

In its simplest form, chromatin consists of the nucleosome core particle, composed of 147 base pairs of DNA wrapped nearly twice around an octamer containing two copies each of the core histones H2A, H2B, H3, and H4.[2] Nucleosomes are assembled into long, linear arrays in which each nucleosome is connected by 10–70 bp of linker DNA, with the length varying between species and cell types.[3] The high affinity of the histone octamer for DNA ensures that nucleosome assembly is a significant barrier for enzymes requiring DNA access, and the folding or compaction of nucleosomal arrays can lead to additional constraints on nuclear processes.[3] Consequently, this necessitates several methods for regulating the positioning and stability of nucleosomes, as well as means to disrupt nucleosomal array condensation. One method is the post-translational modification of histones, which can modulate chromatin folding[4,5] and guide the binding of regulatory proteins.[6,7] Non-allelic variants of the core histones, such as H2A.Z or H3.3, can also be incorporated into nucleosomes, and these variant nucleosomes can have altered stability and/or present novel opportunities for posttranslational modifications.[8,9] The final, and perhaps most potent mechanism, is the use of ATP-dependent chromatin remodeling enzymes that can re-position, evict, or alter the composition of nucleosomes.[10] Indeed, several chromatin remodeling enzymes use the energy of ATP hydrolysis to catalyze the deposition or removal of histone variants, and thus they play an integral role in regulating their chromosomal distributions. There are four subfamilies of ATP-dependent chromatin remodeling enzymes: SWI/SNF, INO80, ISWI, and CHD.[1,10,11] Each family is defined by a characteristic ATPase subunit that is related to the DEAD/H superfamily of DNA helicases, but they also possess unique motifs that mediate binding to nucleosomes and individual complex subunits. As discussed in detail in this review, there exist numerous physical and functional interactions between chromatin remodeling enzymes and histone modifications, creating an intertwined network of mechanisms that control chromatin dynamics.

2. Targeting chromatin remodeling enzymes by histone marks

The majority of histone post-translational modifications occur within the 10–30 amino acid N-terminal domains of each of the histones (often called the histone "tails"). These domains extend from the nucleosomal surface, and although they do not directly contribute to the organization of nucleosomal DNA, the N-terminal tails provide interaction surfaces for a host of nucleosome binding proteins, and are essential for chromatin higher order folding.[3,6] Histone modifications also occur within the globular domains that organize nucleosomal DNA, and given the remarkable number of histone modifications, it may well be that every solvent-exposed histone residue might be a target for modification. Common modifications include lysine acetylation, the mono-, di-, or tri- methylation of lysines, mono- or di-methylation of arginines, the phosphorylation of serines, threonines, or tyrosines, as well as lysine ubiquitylation and SUMOylation.[6] These marks often occur in complex patterns, and there are numerous ongoing studies focused on understanding how such patterns are "read" by cellular machineries.[7] Surprisingly, very few histone marks appear to affect chromatin structure dramatically by themselves (for an exception see Shogren-Knaak et al., 2006[4]),[6]

with the large majority of histone modifications influencing either the binding or activity of other regulatory factors, such as ATP-dependent chromatin remodeling enzymes.

2.1. Bromodomain-acetylated lysine interactions

Since the early studies of Allfrey and colleagues, the acetylation of histone lysines, especially those in the H3 and H4 tails, has been described as a hallmark of transcriptionally active chromatin.[12–14] Since the acetylation of a lysine neutralizes its positive charge, it was long believed that acetylated nucleosomes might be less stable or harbor less tightly bound DNA. These "looser" or "open" structures were proposed to facilitate transcription. Although this simple model is attractive, very little evidence supports this view. High levels of histone acetylation can disrupt chromatin condensation[4,15] and slightly increase the mobility of nucleosomes on DNA,[16] but nucleosomal DNA remains tightly bound to the octamer surface and nucleosome stability appears unchanged. A minor exception is the acetylation of H3-K56 that lies just beneath the first few turns of nucleosomal DNA. In the context of single nucleosomes, this mark slightly enhances the "breathing" of DNA at the very nucleosome edge, though this mark has little effect on the properties of nucleosomal arrays.[17,18]

If histone acetylation is not generally sufficient to disrupt chromatin, then how might this type of mark generate active, open chromatin structures? One dominant mechanism appears to be the recruitment of ATP-dependent chromatin remodeling enzymes that contain subunits harboring acetyl-lysine recognition domains, known as bromodomains.[19] Bromodomains are ~70 kDa and possess a hydrophobic binding pocket formed by an anti-parallel bundle of four α-helices (Fig. 1a).[20,21] The side chain of an acetylated lysine residue inserts into this pocket and is anchored via interactions with bound water molecules and/or an internal asparagine side chain.[20,21] Residues on the surface of the binding pocket may mediate sequence-specific interactions with nearby residues on the histone tail, conferring lysine specificity.[21] Bromodomains often occur within proteins as tandem units, allowing for proteins that recognize multiple acetyl marks on the same or adjacent nucleosomes.[7]

The bromodomain was originally identified as a conserved sequence element of unknown function in a handful of genes including the *Drosophila Brm* and *fsh* genes, the *S. cerevisiae swi2/snf2* and *spt7* genes, and two human genes, *ccg1* and *ring3*.[22,23] Notably, BRM is the catalytic subunit of the Drosophila SWI/SNF remodeling enzyme, also called the PBAP complex. Jeanmougin and coworkers expanded the family and the motif, identifying 37 different members including a number of additional histone acetyltransferases (HATs), as well as the human (BRG1 and BRM) and budding yeast (Swi2/Snf2 and Sth1) homologs of BRM.[24] Indeed, the presence of a bromodomain that is C-terminal to the conserved ATPase domain is a defining feature of the SWI/SNF family of remodeling enzymes.[25]

A functional relationship between histone acetylation and chromatin remodeling was first suggested by genetic experiments in yeast. First, the Gcn5 histone acetyltransferase and the SWI/SNF remodeling enzyme were found to regulate very similar sets of genes, and yeast strains lacking both enzymes were found to be extremely sick or inviable.[26,27] Each of these chromatin enzymes also showed similar genetic interactions with other chromatin components,[28] and chromatin immunoprecipitation studies indicated that the Gcn5 HAT is

required for recruitment of the SWI/SNF enzyme to several inducible genes,[29,30] presumably via the Swi2/Snf2 bromodomain. Likewise, a number of studies found that recruitment of the human SWI/SNF remodeling enzyme to a variety of target genes is also dependent on histone acetylation.[31,32] Indeed, in an elegant study by Thanos and colleagues, it was found that the acetylation of lysines 8 and 12 of the histone H4 tail was specifically required for hSWI/SNF ATPase subunit BRG1's recruitment to the IFN-β gene *in vitro* and *in vivo*, and the *in vitro* interaction could be ablated by the addition of excess competitor BRG1 bromodomain.[33] Of course HATs and remodeling enzymes regulate processes other than transcription, and recent studies indicate that Gcn5-dependent histone acetylation also controls the recruitment of human SWI/SNF to DNA double strand breaks via the bromodomain on the BRG1 ATPase subunit (see additional detail below).[34]

Gcn5 is the catalytic subunit of several HAT complexes, including the SAGA complex, which acetylates histone H3-K4, 9, 14, 18, and 23 within the N-terminal tail.[8,27] Two subunits of the SAGA complex, including Gcn5, contain bromodomains which may help to maintain the enzyme at target loci by interaction with its acetylated nucleosomal products.[35] Workman and colleagues found that histone acetylation by the SAGA complex could promote SWI/SNF recruitment *in vitro*, and that SWI/SNF has a higher affinity for nucleosomes that contain tetra-acetylated H3 tails.[36–38] Specifically, it was found that acetylated nucleosomes slowed the dissociation of SWI/SNF from arrays.[36–38] These biochemical studies lend strong support to the view that histone marks, such as lysine acetylation, may "recruit" factors primarily by slowing their off-rate rather than promoting their initial association with a target locus. This view is supported by further genetic studies in yeast where removal of the Swi2/Snf2 bromodomain disrupts recruitment *in vivo*,[38] though it is not entirely eliminated. In contrast, inactivation of SWI/SNF domains that mediate interactions with site-specific transcriptional activators has a much more severe effect on SWI/SNF function and recruitment.[39,40] These studies suggest a unified view in which chromatin remodeling enzymes, such as SWI/SNF, are initially recruited to regulatory regions via interactions with site-specific DNA binding factors, and the subsequent interactions between bromodomains and acetylated histones stabilize chromatin associations, leading to stable nucleosome interactions that may be more productive for remodeling.

Whereas removal of the sole bromodomain within yeast SWI/SNF does not have dire consequences, the bromodomains within the related RSC remodeling enzyme play essential roles. Like SWI/SNF, mutations that affect the RSC complex are synthetically inviable in combination with inactivation of Gcn5, and RSC has also been shown to bind tetra-acetylated H3 nucleosomes *in vitro*.[41,42] However, unlike the yeast SWI/SNF complex, the RSC complex and its fly and mammalian counterparts, PBAP and PBAF, have multiple bromodomains.[43,44] Indeed, the namesake subunit of PBAP and BPAF is called Polybromo after its six bromodomains (Polybromo is also known as BAF180).[45] This subunit appears to be an evolutionary fusion of the Rsc1, Rsc2, and Rsc4 subunits of yeast RSC which each have two bromodomains.[46] Human SWI/SNF also appears to contain additional bromodomain-containing subunits, Brd7 and Brd9.[46] Together with the single bromodomain

within the catalytic subunit, these remodeling enzymes may contain between 4 and 10 bromodomains!

Why so many acetyl-lysine recognition modules? Some bromodomains may act in a redundant fashion, or they may bind different acetylated residues on adjacent nucleosomes or even on nearby transcription factors. Some bromodomains are clearly not redundant, as genetic studies have shown that one of the two bromodomains within both yeast Rsc1 and Rsc2 (which are mutually exclusive subunits of RSC) are essential for RSC function, and deletion of either tandem bromodomain within yeast Rsc4 also inactivates RSC function in vivo.[47] One of the two bromodomains in Rsc4, and one of the six bromodomains in Drosophila Polybromo has been shown to bind specifically to H3-K14ac, and *in vitro* studies have demonstrate that H3-K14ac can recruit yeast RSC to nucleosomal substrates.[16,41]

Interestingly, work from the Cairns lab has shown that the multiple bromodomains within yeast RSC are involved in an autoregulatory mechanism that is controlled by the Gcn5 HAT.[43] In addition to its typical substrate, the H3 tail, Gcn5 also acetylates K45 of Rsc4.[43] The Rsc4-K45ac mark creates an intramolecular binding site for the first bromodomain of Rsc4, and this binding event blocks the second bromodomain from binding H3-K14.[43] This implicates Gcn5 in both the positive and negative regulation of RSC, and suggests that bromodomain function is not confined simply to recruitment events.

Although bromodomains are generally a feature of the SWI/SNF family of remodeling enzymes, the yeast SWR-C also possesses two bromodomains within its subunit Bdf1.[48] SWRC is a member of the INO80 family of remodeling enzymes that catalyzes the ATP-dependent exchange of H2A/H2B dimers for H2A.Z/H2B dimers, leading to targeted deposition of the H2A.Z histone variant within promoter proximal nucleosomes.[49–51] This H2A.Z deposition reaction is greatly stimulated by histone H4 acetylation *in vitro*,[48] and studies have indicated that the NuA4 HAT plays a key role in H2A.Z deposition by SWR-C *in vivo*.[52] Recent studies from Wu and colleagues suggests a model in which SWR-C is targeted to nucleosome free regions upstream of RNA polymerase II promoters, and then it preferentially interacts with an adjacent, acetylated nucleosome via its Bdf1 subunit which then targets that nucleosome for efficient H2A.Z deposition.[53] This model is consistent with a general theme that histone marks serve as a mechanism to fine-tune the positioning of a chromatin remodeling enzyme, rather than functioning as the primary method of recruitment.

2.2 Chromatin remodeling enzymes that bind methylated lysines

In contrast to lysine acetylation, the mono-, di-, or trimethylation of lysine residues does not neutralize their positive charge, and thus studies have long focused on identifying domains and proteins that recognize these marks rather than speculating on direct changes to chromatin structure.[6] Furthermore, whereas lysine acetylation is generally a hallmark of transcriptionally active chromatin, lysine methylation appears in both active and inactive chromatin domains. For instance, repetitive DNA sequences that are packaged into condensed, heterochromatic domains are enriched in H3-K9 di- and tri-methylation, and developmentally silenced loci contain H3-K27 dimethylation.[54] In contrast, actively

transcribed genes contain nucleosomes that are di- and tri-methylated at H3-K4, K36, and K79.[54] H3-K4me2/3 is enriched at the 5' end of transcribed genes, whereas H3-K36me2/3 and K79me2/3 are enriched in gene bodies.[6,54,55] As for acetyl lysine, both the "active" and "inactive" methyl marks are targets for chromatin remodeling enzymes.

The two most common methyl-lysine binding domains found in chromatin remodeling enzymes are plant homeodomain (PHD) fingers and chromodomains.[7] A third common methyl lysine binding domain, called Malignant Brain Tumor (MBT) repeats, has not as yet been identified in remodeling enzymes, but to date this domain is restricted to factors involved in chromatin silencing (e.g. L3MBTL1).[56-58] The first chromodomains were identified in the heterochromatin structural proteins, Polycomb and heterochromatin protein 1 (HP1).[59] Chromodomains bind methyl-lysine side chains in a cage formed by aromatic residues along an anti-parallel β-sheet,[60,61] whereas PHD finger domains consist of a two-stranded β-sheet and one or more α-helices coordinated by zinc ions (Fig. 1b–c).[62] As in chromodomains, the methyl-lysine side chain binds within the β-sheet in a pocket lined by aromatic residues.[7] In addition to the recognition of methylated lysines, some chromodomains can also bind to DNA and RNA, leading to the proposal that the chromodomain may have evolved from an ancestral fold with a wide-target specificity.[63] Similarly, a PHD finger from the Msc1 subunit of the fission yeast SWR-C remodeling enzyme also exhibits E3 ubiquitin ligase activity, suggesting that PHD fingers can also have multiple functions.[64]

The CHD family of chromatin remodeling proteins is highly conserved from yeast to human. The distinguishing characteristic of this family is the presence of N-terminal, tandem chromodomains in addition to a C-terminal Swi2/Snf2 ATPase domain.[1,65] There are three subfamilies of CHD proteins, the Chd1–2 family, the Chd3–4 family (also known as Mi-2α and Mi-2β), and the Chd5–9 family.[1,65] The Chd1 and Chd2 proteins contain an additional DNA binding domain at their C-terminus, whereas Chd3–4 members contain one or more PHD fingers.[1,65] The Chd5–9 family is more diverse and harbors other types of motifs, such as SANT domains that can interact with unmodified histone tails.[66] The chromodomains of mouse and possibly *Drosophila* Chd1 are required for normal nuclear localization patterns and are essential for enzymatic activity,[67-69] and the chromodomain and PHD fingers of Chd3/4 members are important for nucleosome binding and chromatin remodeling activities.[69]

Similar to SWI/SNF family members, some CHD remodeling enzymes are recruited to target loci by a combination of site-specific DNA binding proteins and histone modifications. For example, the NuRD complex is a multi-subunit remodeling enzyme conserved from flies to humans that harbors a Chd3/4 family member.[65,70] NuRD enzymes are targeted by a variety of site-specific DNA binding proteins to repress transcription of genes during development. For example, the *Drosophila* NuRD complex is recruited by the hunchback (Hb) repressor to repress HOX gene transcription,[71] and mammalian NuRD complexes interact with a variety of transcriptional repressors to regulate lineage commitment and differentiation of specific cell types.[72-74] In addition to binding transcription factors, the PHD fingers of Chd3/4 members interact with H3 peptides methylated at either K9 or K36, and these interactions can be regulated by the methylation

state of H3-K4.[70,75] Like the case for SWI/SNF family members, it seems likely the recognition of histone marks by PHD fingers functions to stabilize a CHD family member at a chromatin locus following its initial recruitment.

Human Chd1 binds H3-K4me2/3 via one of its two chromodomains which helps to target it to active genes where it facilitates transcription.[76,77] It is controversial whether yeast Chd1 is able to recognize H3-K4me, as its chromodomains lack one of the aromatic residues necessary for binding, and conflicting studies report on yChd1 interactions with the H3 tail.[54,76–78] However, yeast Chd1 is known to associate with the SAGA and SLIK complexes, and thus yChd1 may be the factor that allows these HATs to target H3-K4me nucleosomes for H3 acetylation.[76] Nevertheless, from yeast to mammals, Chd1 is recruited to the 5' end of active genes via interactions with transcriptional initiators such as Mediator and PAF1, where its remodeling activity facilitates nucleosome turnover and gene expression.[79,80] Intriguingly, recent evidence also suggests that yChd1 may work in conjunction with the ISWI family of remodeling enzymes to inhibit cryptic transcription in gene bodies by stabilizing nucleosomes harboring H3-K36me (see discussion in Section 5.2., below).

Several members of the ISWI family of remodeling enzymes contain subunits harboring PHD fingers that interact with H3-K4me3. For instance, the human NURF complex, a member of the ISWI family of ATP-dependent chromatin remodelers, recognizes H3-K4 methylation through its subunit BPTF.[81] Interestingly, BPTF contains both a bromodomain and a PHD finger domain separated by an α-helical linker.[82] When the PHD finger is bound to an H3-K4me3 nucleosome, the bromodomain selectively binds acetylated H4-K16 on the same nucleosome, and, in fact, this binding is cooperative.[83] When both marks are bound, the linker region of BPTF can be positioned into the groove of DNA, a contact which may be involved in the remodeling mechanism.[84] NURF is implicated in the transcriptional activation of genes during development, as its deletion leads to developmental defects in flies and frogs and is embryonic lethal in mice.[85–87] Somewhat paradoxically, NURF's specific association with nucleosomes requires active transcription, as H3-K4 methylation occurs during or immediately following elongation.[54] However, since NURF also interacts with other transcriptional activators, it may be recruited to promoters by these other factors, where it can then assist in the remodeling of H3-K4me/H4-K16ac nucleosomes for rapid re-initiation. This theory is supported by NURF's known role in the expression of inducible genes, such as heat shock protein genes in flies.[85]

3. Remodeling complexes that establish or remove histone marks

Although chromatin remodeling enzymes are defined by their ATP-dependent activities, several enzymes contain additional subunits with enzymatic activities that directly modulate histone modifications. As discussed below in four examples, these novel activities can regulate or target a chromatin remodeling event or further reinforce the desired transcriptional outcome.

3.1. Histone acetylation: The Tip60 complex

Tip60 was initially identified as a protein that interacted with the HIV transactivator, Tat,[88] and functions as a transcriptional coactivator for a host of regulatory factors,[89] including many nuclear hormone receptors.[90] Subsequently Tip60 was shown to be one of the founding members of the MYST family of histone acetyltransferases that acetylate N-terminal lysine residues within histones H4 and H2A.[91] Biochemical studies discovered that Tip60 is a subunit of a large protein complex that also contains a member of the INO80 family of ATPases, p400/domino, that is most highly related to yeast Swr1.[92,93] Indeed, an elegant study from the Cote group demonstrated that the mammalian Tip60 complex is a physical merger of the essential yeast NuA4 HAT and SWR-C chromatin remodeling complexes that links histone acetylation to the ATP-dependent deposition of the H2A.Z histone variant.[94] In this case, H4 acetylation not only enhances the binding of the complex to target nucleosomes via the bromodomain subunit, Bdf1 (Brd8 in humans), but acetylation also appears to directly stimulate the dimer exchange reaction.[48] Interestingly the Tip60 HAT also harbors a chromodomain that appears to target this enzyme complex to histone H3-K9me2 at sites of DNA damage (Fig. 2a). Indeed, studies in *Drosophila* cells showed that Tip60 associates with DNA double strand breaks, where it acetylates the DNA damaged-induced, phosphorylated form of histone H2A.X, leading to its subsequent replacement with H2A.[93] Recent studies of Tip60 have focused on embryonic stem cells, where the HAT activity of Tip60 plays a key role in stem cell maintenance and the repression of many developmental genes by the master regulator, Nanog.[89]

3.2. Histone deacetylation: NuRD and SMARCAD1

As discussed above, the NuRD complex is a highly conserved remodeling enzyme that functions in myriad transcriptional repression pathways during development. In addition to its Chd3/4 ATPase subunits that interact with H3-K9 or K36, the NuRD complex also contains two histone deacetylase subunits, HDAC1 and HDAC2, which target "active" histone acetyl-lysine marks for deacetylation (Fig. 2b).[70] Interestingly, HDAC activity is stimulated by ATP hydrolysis, implicating nucleosome remodeling as an essential step in this process.[95,96] A role for NuRD in establishing and maintaining repressive chromatin structures is further reinforced by the Mbd2 and Mbd3 subunits that interact with CpG methylated DNA.[97,98] The ability of NuRD ability to modulate gene expression is important in regulating pluripotency and cell fate decisions in hematopoietic and embryonic stem cells.[74] NuRD also associates with pericentric heterochromatin during S phase, where it forms higher-order chromatin structures necessary for S phase progression.[99,100] Consistent with these activities, the loss of NuRD subunits is associated with both normal and premature aging.[101]

The mammalian SMARCAD1 remodeling enzyme also harbors the HDAC1 and HDAC2 deacetylase subunits.[102] SMARCAD1 is brought to replicating regions via direct interaction with the replicative clamp, PCNA, where it deacetylates the newly deposited H3 and H4 histones (Fig. 2c).[103] In combination with the subsequent methylation of H3-K9, these hypoacetylated nucleosomes facilitate an environment favorable to chromatin compaction and binding by heterochromatin proteins such as HP1, and thus SMARCAD1 functions to maintain heterochromatic regions during S phase.[103] Congruently, inactivation of

SMARCAD1 leads to hyperacetylation, chromosome segregation defects, and genome instability.[103] Recently, SMARCAD1 and its budding yeast homolog Fun30 have also been implicated in promoting DNA processing at DNA double strand breaks,[104,105] although the exact mechanism remains unknown.

3.3. Histone deubiquitylation: hINO80

The mono-ubiquitylation of lysine residues within the C-terminal tail domains of histones H2A and H2B occurs within both transcriptionally active chromatin domains and near sites of DNA double strand breaks.[9] The mono-ubiquitylation of H2B-K123 is essential for establishing methylation of H3-K4 and H3-K79, and represents one of the best examples of histone modification crosstalk.[106] Whereas histone deacetylases work in opposition to HATs, a large family of deubiquitylating enzymes (DUBs) functions to remove ubiquitin marks from proteins, including histones. Typically, DUBs physically interact with the proteasome machinery, and function to recycle ubiquitin molecules prior to ubiquitin-dependent degradation.[107] Proteomic studies identified the DUB, Uch37, as an integral subunit of the human INO80 complex, where it associates with the DNA-binding subunit NFRKB.[108] When present in hINO80, Uch37 is blocked from binding its ubiquitin substrate, but when Uch37 comes into contact with Rpn13, the 19S proteasome ubiquitin receptor, the DUB activity of Uch37 activity is activated.[108] This interaction with Rpn13 is transient, occurs at the auto-inhibitory c-terminal tail of Uch37, and does not disrupt Uch37's incorporation into INO80.[108] Although the ubiquitylated substrate for Uch37 is unknown, its incorporation into the hINO80 complex makes a strong case that it may act on H2A-ub and/or H2B-ub (Fig. 2d).[107] Current models propose that the DUB activity of hINO80 may play a key role in promoting transcriptional activation and DNA repair.

4. Histone marks that regulate remodeling enzyme activity

Chromatin remodeling enzymes make intimate contacts with their nucleosomal substrates, and thus it seems likely that they would take advantage of histone posttranslational modifications as a regulatory mechanism. Since the early genetic interactions were identified between SWI/SNF and the Gcn5 HAT,[28] many studies have tested whether histone acetylation impacts ATP-dependent remodeling reactions. Generally, however, histone hyperacetylation does not have a dramatic impact on the ATPase or nucleosomal array remodeling activities of many enzymes, including yeast and human SWI/SNF, *Xenopus* NuRD (xMi-2), yeast RSC, or *Drosophila* CHRAC.[11] Early work, though, showed that histone hyperacetylation inhibits the ability of ySWI/SNF to remodel multiple nucleosomal arrays (catalytic array remodeling), likely due to bromodomain effects on binding affinity.[109] In contrast, several members of the ISWI family of enzymes are inhibited by histone hyperacetylation, such as Drosophila NURF,[11] and yeast Chd1 and Isw2,[16] due in part to acetylation of histone H4-K16 (see below).

Whereas early studies employed hyperacetylated histones isolated from cells treated with histone deacetylase inhibitors (e.g. butyrate), more recent studies have used native ligation methods to generate histones that are acetylated at defined locations.[16,42] In this case, it was found that H4 acetylation, but not H3, altered the proportion of remodeled products by the yeast RSC enzyme, due to enhanced octamer transfer in *trans*.[16] Furthermore,

hyperacetylation of histone H3, but not H4, enhanced the ability of ySWI/SNF and yRSC to slide nucleosomes in *cis* and to evict H2A/H2B dimers.[42] Interestingly, in the case of ySWI/SNF, these stimulatory effects required the Swi2/Snf2 bromodomain.[42] Thus, these data indicate that bromodomainacetyl lysine interactions may not solely influence binding affinity, but also alter remodeling activity.

4.1. H4 K16 acetylation

There are two clear examples where a single histone mark can impact a remodeling enzyme. The first is the inhibitory effect of H4-K16ac on the activity of ISWI family members. Genetic studies in *Drosophila* demonstrated that overexpression of the MOF acetyltransferase, the enzyme that catalyzes H4-K16ac, enhances the phenotype of an ISWI mutant, whereas inactivation of MOF alleviates the X-chromosome condensation phenotype of an ISWI mutant.[110] Consistent with these genetic studies, the ISWI subfamily of remodeling enzymes requires the histone H4 N-terminal tail to mobilize nucleosomes in *cis*, and this activity is reduced ~4-fold by histone H4-K16ac.[4] Recent studies indicate that this requirement for the H4 tail, and the inhibition by H4-K16ac, is due to an auto-inhibitory mechanism in which an ISWI domain (called AutoN) mimics the H4 tail and occludes the ATPase domain. This inhibitory domain is only released after engaging the H4 tail of a nucleosomal substrate (Fig. 3a).[111,112] Indeed, removal of the ISWI AutoN domain creates an ISWI enzyme that no longer requires the H4 tail for activity.[111–113] A similar auto-regulatory mechanism also appears to control the activity of yeast Chd1 which is also most active when bound to nucleosomes with an intact H4 tail.[112,114]

4.2. H3 K56 acetylation Histone

H3 is acetylated at K56 prior to being incorporated into nucleosomes, making it a mark of newly deposited nucleosomes.[115,116] As a result, H3-K56ac is highly enriched within newly replicated chromatin and at gene promoters where nucleosomes are rapidly exchanged.[117,118] Genetic studies have shown that the levels of H3-K56ac are important for maintenance of genome stability, and loss of H3-K56Ac also affects the regulation of a subset of inducible genes.[119,120] H3-K56Ac was initially believed to be a histone mark that was unique to fungi, though more recent studies have found that this mark also occurs in mammalian cells,[121] including embryonic stem cells.[122] Unlike many histone marks, H3-K56 is located within the globular core of H3, on the surface of the nucleosome near the entry-exit point of DNA.[2] H3-K56 is engaged in a water-mediated contact with the last turn of nucleosomal DNA, and its location led to the hypothesis that the loss of positive charge upon acetylation might reduce the interaction between histones and DNA, creating a less stable nucleosome.[18] However, FRET experiments designed to measure nucleosomal breathing found only a modest effect of H3 K56ac, crystal structures bearing H3-K56Q or K56E substitutions showed no difference in nucleosome structure, and an H3-K56Q substitution did not disrupt 30 nm fiber compaction.[17,18]

Although H3-K56Ac does not seem to alter nucleosome structure, this mark does impact the functioning of several chromatin remodeling enzymes. First, it was found that H3-K56Ac has a modest effect on the rate of nucleosome remodeling by the yeast SWI/SNF and RSC enzymes (~1.4-fold increase),[18] presumably due to the slight weakening of entry-exit DNA

contact with the histone octamer. However, much more dramatic effects have been observed on the activity of INO80 family members.[123] Remarkably, this single histone mark switches the substrate specificity of the yeast SWR-C complex, allowing it to catalyze the deposition of H2A/H2B dimers as well as H2A.Z/H2B dimers (Fig. 3b).[123,124] H3-K56Ac also enhances the ability of the INO80 complex to evict H2A.Z/H2B dimers from nucleosomal substrates.[123] Further mechanistic studies suggest that H3-K56Ac functionally interacts with the Swc2 subunit of SWR-C and that it alters the ability of the enzyme to discern a nucleosomal substrate from a remodeling product.[123] Consequently, when SWR-C acts on an H3-K56Ac nucleosome, it appears to remove an H2A.Z/H2B dimer from its product, replacing it with an H2A/H2B dimer, creating a cycle of continuous dimer exchange.[123] In vivo, constitutive H3-K56ac decreases the level of H2A.Z. at promoters throughout the yeast genome, consistent with H3-K56ac disrupting SWR-C activity.[123]

5. Multi-faceted interactions

The preceding sections have dealt with cases in which histone modifications and chromatin remodeling enzymes have direct, physical interactions that lead to functional consequences. In some other cases, however, the interactions are not direct, but rather the outcome of a chromatin remodeling event can alter a subsequent histone modification. One simple example that we will not discuss in detail would be a scenario in which a chromatin remodeling event promotes the binding of a site-specific DNA binding factor that subsequently recruits a histone modification enzyme (for example, see Cosma et al., 1999; Krebs et al., 1999).[29,125]

5.1. Chromatin remodeling and histone mark dynamics at DNA double-strand breaks

The formation of a DNA double-strand break (DSB) can be a catastrophic event during which the cell cycle is arrested and numerous proteins are recruited to mediate its repair, including many chromatin remodeling and histone-modifying enzymes. Although headway has been made in uncovering the roles of some of these proteins in the DSB response, the function of many chromatin modifiers remains unclear (for a review, see Papamichos-Chronakis and Peterson, 2013).[9,126] One of the earliest signs of a DSB is the widespread phosphorylation of the histone variant H2A.X. at S129 in yeast and at S139 in mammals (often referred to as γ-H2A.X).[127,128] Other histone marks associated with open chromatin structure also accumulate rapidly around DSBs, including H3-K4me3 and H2A and H2B ubiquitylation within their C-terminal domains.[9]

Some of the many chromatin remodeling complexes recruited to a DSB are SWI/SNF family members (ySWI/SNF and RSC in yeast or BAF in mammals). In mammalian cells, recruitment of the BAF complex requires γ-H2A.X, even though BAF does not appear to bind this mark directly.[129] Furthermore, in the absence of the BAF complex, the domain of γ-H2A.X within DSB chromatin does not spread normally and it does not persist.[34,129] Interestingly, Kwon and colleagues find that γ-H2A.X also recruits the human Gcn5 HAT and that the Gcn5-dependent acetylation of H3 promotes BAF recruitment via its associated bromodomain.[34] In this case, the subsequent chromatin remodeling directed by BAF is proposed to increase the accessibility of neighboring nucleosomes, enhancing H2A.X phosphorylation, and as a result, more extensive H3 acetylation and BAF binding (Fig.

4a).[34] In this way, γ-H2A.X formation leads to a cooperative feed forward loop in which it is able both to propagate itself and to initiate chromatin remodeling around DSBs.

A similar mechanism appears to control recruitment of the ISWI homolog, Snf2H, to mammalian DSBs. In this case the Rnf20/Rnf40 E3 ubiquitin ligase heterodimer ubiquitylates H2B-K120 at DSBs, and H2B-K120ub is required for efficient methylation of H3-K4 by the Set1 enzyme.[130] H3-K4me then promotes the binding of SNF2H, a human homolog of Isw1 present in the ACF chromatin remodeling complex (Fig. 4b).[130] Depletion of SNF2H prevents the formation of RPA, Rad51, and BRCA1 foci around a DSB,[130] indicating that this histone modification-chromatin remodeling regulatory loop plays a key role in early recruitment of repair factors.

5.2. Chromatin dynamics during transcription elongation

During transcriptional elongation, nucleosomes are removed in front of the elongating RNA Polymerase II (RNAPII) and then rapidly reassembled after its passage.[131] The Set2 methyltransferase is believed to travel with RNAPII whereby it methylates newly deposited nucleosomes at H3-K36; consequently, the level of H3 K36me2/3 within a gene body corresponds to its expression level.[132–134] The re-assembly of nucleosomes following RNAPII passage is also associated with deposition of histones that harbor lysine acetylation marks typical of newly replicated chromatin.[116,135] If allowed to persist, these acetyl marks appear to promote cryptic transcription within gene bodies.[136,137] To counteract these deleterious effects, the Rpd3S deacetylase complex uses both the chromodomain in its subunit Eaf3 and the PHD finger in its subunit Rco1 to target HDAC activity to H3-K36me2/3 nucleosomes within gene bodies.[138]

Several lines of evidence have also suggested a role for the ISWI and Chd1 remodeling enzymes in controlling Rpd3S activity within gene bodies. Like Set2 methyltransferase, the Isw1 and Chd1 remodeling enzymes are required to inhibit histone acetylation and cryptic transcription within actively transcribed genes.[139] The ISW1b complex, via its PHD-finger subunit, Ioc4, and Chd1 (presumably via its chromodomain) interact with H3-K36me3 nucleosomes, and ISW1b co-localizes with H3-K36me *in vivo*.[139,140] Recently, the Li group has demonstrated that CHD and ISWI remodeling enzymes facilitate Rpd3S activity by spacing nucleosomes 30–40 base pairs apart, allowing Rpd3S to bridge two adjacent nucleosomes (Fig 4c).[141] The ability of Rpd3S to bind two nucleosomes at once allows it to target both H3-K36me nucleosomes and their neighbors for deacetylation, allowing for the efficient stabilization of nucleosomes, even when chromatin domains are not saturated by the methylation mark.[142] Similarly, in mammalian cells, Chd1 has been implicated in stabilizing nucleosome occupancy in gene bodies by mediating H2B ubiquitylation at K123 and K120 by the Rad6 and Bre1 enzymes.[55,143] The ability of ISW1 and CHD family remodeling enzymes to slide nucleosomes to the preferred spacing of complexes that bind multiple nucleosomes (and, conversely, to move them outside the preferred linker length to inhibit binding) may be one of their primary functions *in vivo*.

6. Perspective

Since the identification of the first ATP-dependent remodeling enzyme[144–146] and first nuclear histone acetyltransferase,[147] there has been a wealth of both data and speculation on interactions between these two classes of chromatin enzymes. The number of chromatin remodeling enzymes and the diversity of histone modifying enzymes is now staggering, but we continue to see more examples of how these enzyme families functionally interface with each other. As illustrated throughout this review, histone marks can directly influence both the targeting and activity of remodeling enzymes, and chromatin remodeling enzymes can potentiate histone marks by both direct and indirect mechanisms. It seems apparent that these two families of enzymes have evolved to work together in the control of all nuclear events.

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Highlights

- Chromatin modifications and remodeling act in concert to alter chromatin structure.

- Remodeling enzymes have specialized binding domains for targeting histone marks.

- Some remodeling complex subunits can establish or remove histone marks.

- Histone modifications can regulate remodeling enzyme activity and specificity.

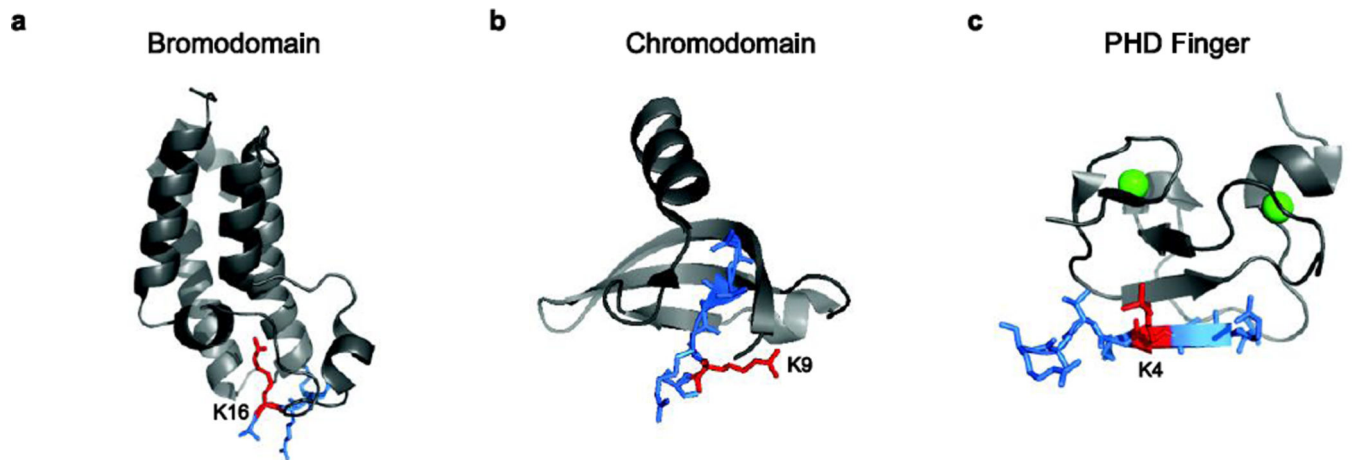- Many processes consist of a plethora of histone modification and remodeling events.

Figure 1. Chromatin remodeling enzymes have specific domains that bind histone modifications
(a) Bromodomains bind acetylated lysines. The bromodomain of Gcn5 bound to an H4 tail peptide acetylated at K16 (PDB: #1E6I). **(b)** Chromodomains bind methylated lysines. The chromodomain of HP1 protein Swi6 bound to an H3 tail peptide methylated at K9 (PDB: #1KNA). **(c)** PHD fingers bind methylated lysines. The PHD finger domain of ING2 bound to an H3 tail peptide methylated at K4 (PDB: #2G6Q).
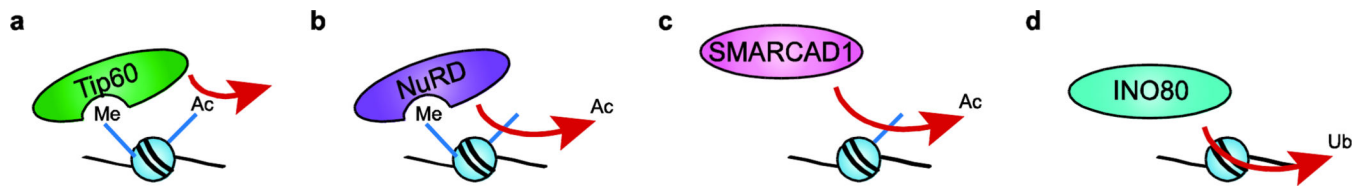
Figure 2. Chromatin remodeling enzymes can modify histone marks
(a) Tip60 binds H3-K9me nucleosomes and acetylates H4 tails. **(b)** The NuRD complex binds H3-K9me nucleosomes and deacetylates them. **(c)** SMARCAD1 deacetylates newly-deposited nucleosomes during replication via association with subunits HDAC1 and HDAC2. **(d)** The Uch37 subunit of human INO80 has been recognized to posses DUB activity that may allow INO80 to target nucleosomes for deubiquitylation.
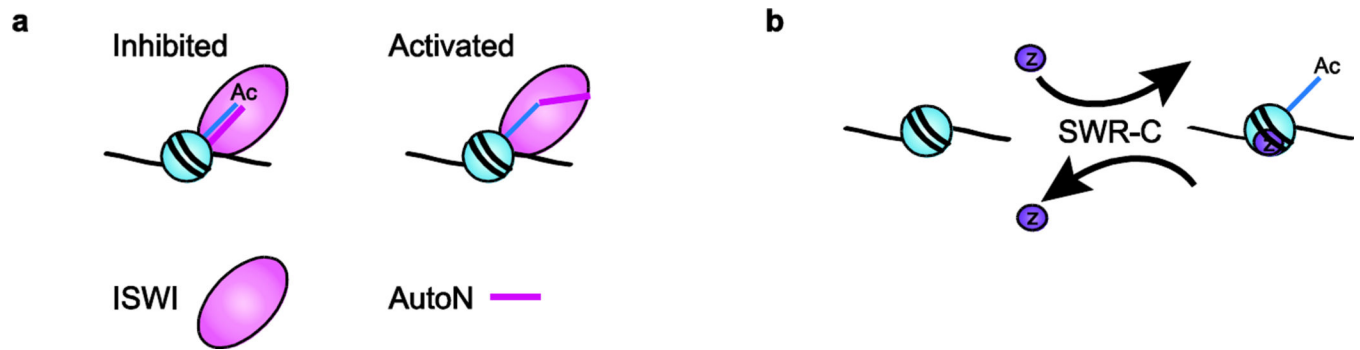
Figure 3. Histone modifications can regulate chromatin remodeling activity

(a) ISWI contains a regulatory region homologous to the H4 tail, called AutoN, which binds the ATPase domain and inhibits activity. When ISWI binds the H4 tail, AutoN is displaced and ATPase activity resumes. However, H4 tails acetylated at K16 do not displace AutoN, and consequently inhibit ISWI function. **(b)** SWR-C exchanges H2A/H2B dimers for dimers containing H2A.Z. However, the presence of H3 K56ac alters the substrate specificity of SWR-C, allowing it to exchange dimers in both directions.
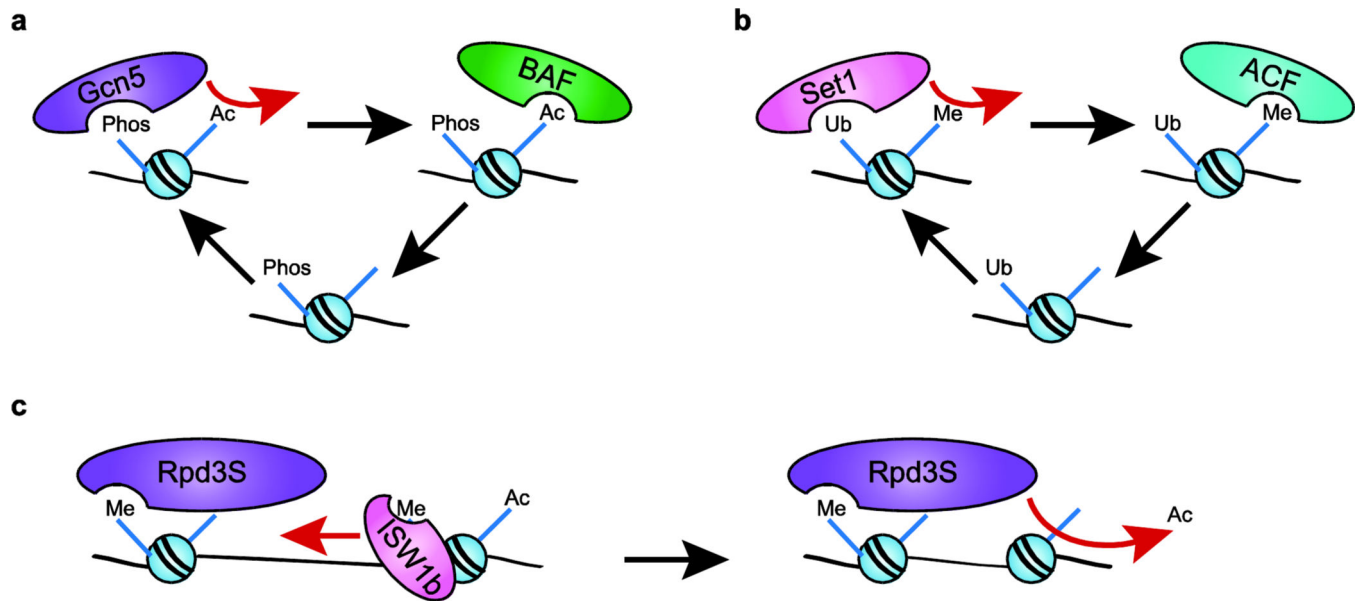
Figure 4. Histone modifications and chromatin remodeling enzymes exhibit complex interactions
(a) At DSB's, γ-H2A.X recruits Gcn5 to nucleosomes, where it acetylates the H3 tail and consequently favors BAF binding. BAF then remodels nearby nucleosomes, leading to spreading of the γ-H2A.X mark and continuation of the cycle. **(b)** H2B ubiquitylation at a DSB recruits Set1, which methylates H3 K4, leading to binding by the ACF subunit SNF2H. The remodeling enzyme then remodels nearby nucleosomes in a way that favors spreading of the ubiquitin mark. **(c)** H3-K36me nucleosomes are targeted by Rpd3S for deacetylation in gene bodies. ISWI1b and CHD1 space methylated nucleosomes preferentially for Rpd3S binding to two nucleosomes at once.