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Transcription-associated histone modifications & cryptic transcription

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Abstract

Eukaryotic genomes are packaged into chromatin, a highly organized structure consisting of DNA and histone proteins. All nuclear processes take place in the context of chromatin. Modifications of either DNA or histone proteins have fundamental effects on chromatin structure and function, and thus influence processes such as transcription, replication or recombination. In this review we highlight histone modifications specifically associated with gene transcription by RNA polymerase II and summarize their genomic distributions. Finally, we discuss how (mis-)regulation of these histone modifications perturbs chromatin organization over coding regions and results in the appearance of aberrant, intragenic transcription.

1. Introduction

Chromatin is a nucleoprotein complex built from nucleosomal repeat units. Nucleosomes themselves consist of 147 bp of DNA wrapped 1.7 times around a histone octamer core particle (two copies of histones H2A, H2B, H3 and H4 each) [1]. Chromatin not only allows for the compaction of DNA within the nucleus, it also ensures that a large fraction of genomic DNA is not readily accessible and thus has drastic consequences for the regulation of gene expression. Transcription, as well as other cellular processes, require a veritable arsenal of factors in the form of activators and repressors that enable correct temporal and spatial access to specific DNA sequences. Nucleosome dynamics, histone modifications and chromatin remodeling are three aspects of chromatin structure that are closely interlinked, and perturbation in any one part can have severe consequences for a number of cellular processes.

2. The basics of RNA polymerase II transcription

2.1 Transcription of chromatin

Polynucleosomes are extremely stable and represent the first order of packaging, often referred to as “beads-on-a-string” or 11 nm fiber [2]. While further compaction of chromatin into higher order structures does take place, most chromatin is transcribed in this

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configuration. Nucleosomes represent a major barrier for Pol II transcription *in vivo* and *in vitro*. Unlike phage SP6 RNA polymerase or yeast Pol III, Pol II cannot transcribe efficiently through an intact nucleosome by itself but requires additional factors that enable it to overcome the barrier represented by nucleosomes [3, 4].

2.2 Pol II transcription cycle

Transcription by Pol II (reviewed in [5]) is initiated by activator proteins binding upstream of the core promoter and signals for the subsequent recruitment of coactivators such as mediator or the SAGA histone acetyltransferase (HAT), as well as chromatin remodelers whose function it is to alter chromatin architecture for assembly of the general transcription machinery. A series of protein-protein interactions results in the recruitment of Pol II and general transcription factors (GTFs) TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH and formation of the pre-initiation complex (PIC). Following PIC assembly, the DNA at the transcription start site (TSS) is unwound by Rad25 (human XBP of TFIIH), thus allowing the single-stranded DNA template to be positioned in the Pol II active site. Concomitantly, the carboxy-terminal heptad repeat sequences (C-terminal domain; CTD) of Rpb1, the largest Pol II subunit, are phosphorylated by Kin28 (CDK7 in human TFIIH) specifically on Ser5. Pol II then loses contact with some GTFs and escapes into early elongation.

Efficient elongation requires a further phosphorylation step by Ctk1 (human P-TEFb) on the Ser2 position of the Pol II CTD that helps to recruit factors important for transcription elongation, termination and mRNA processing as well as histone modifiers and remodelers. Throughout the transcriptional cycle the Pol II CTD – whether phosphorylated or not – functions as a recruitment platform for a large number of stage-specific factors required for efficient transcription.

3. Influencing nucleosome dynamics

3.1 Chromatin remodeling and histone dynamics

One way of changing chromatin structure is by using chromatin remodelers. This class of enzymes uses the energy of ATP hydrolysis to break existing DNA-histone contacts in order to slide or evict histones/nucleosomes from the DNA (reviewed in [6]). Nucleosomes are turned over at different rates depending on their genomic location as well as on their modification status [7]. Several studies have shown that H2A/H2B dimers are rapidly exchanged in and out of existing nucleosomes over transcribed regions [8, 9]. In contrast, histone exchange of H3/H4 tetramers occurs at high rates over the promoters of actively transcribed genes, but is limited to highly transcribed genes over ORFs [8, 10, 11]. This is linked to the observation that *in vitro* Pol II can transcribe through hexasomal nucleosomes following the eviction of a single H2A/H2B dimer, while the H3/H4 tetramer is retained on the DNA [12, 13]. Only in highly transcribed genes that contain multiple elongating Pol II molecules is there evidence to suggest complete dissociation of histone octamers from the DNA over coding regions, which are subsequently reassembled in the wake of Pol II passage. Both eviction and reassembly of nucleosomes depend on histone chaperones, such as Asf1, Nap1, Spt6 or FACT which often work in conjunction with remodeling complexes [14-20].

3.2 Histone variant incorporation

Apart from the canonical versions of histone proteins, there are several variant forms that perform specialized functions. Variants can differ in histone tails, histone fold domains or amino acid sequence. In higher eukaryotes histone H3.3 is incorporated preferentially over transcribed regions independent of DNA replication [21]. Interestingly, the single version of histone H3 present in yeast most closely resembles the H3.3 variant rather than the replication-dependent H3.1 [22].

Histone H2A.Z (Htz1 in yeast) is another important histone variant involved in a variety of different and sometimes opposing processes. Initially identified in preventing the spread of heterochromatin to euchromatic regions [23, 24], it is involved in gene activation, gene silencing, nucleosome turnover, chromosome segregation and differentiation (reviewed in [25]). H2A.Z is highly conserved from yeast to humans. It is not essential in yeast, although deletion of *HTZ1* results in transcriptional defects [26, 27]. However, loss of H2A.Z is lethal in higher eukaryotes [25]. Genome-wide studies have found H2A.Z associated with promoters at practically all +1 nucleosomes (relative to the transcription start site) and also at a large proportion of −1 nucleosomes [28-33]. A similar pattern is also found in human cells, although enhancers and insulators are also marked by H2A.Z [34]. Interestingly, in *Drosophila* H2A.Z associates only with the +1 nucleosome [33].

The involvement of H2A.Z in transcription regulation has been clearly established, yet the mechanistic details remain a focus of ongoing research. Suggestions range from H2A.Z-mediated effects on nucleosome stability, nucleosome positioning and establishing contacts with the transcriptional machinery to maintaining active genes close to the nuclear periphery [27, 30, 31, 35, 36]. In yeast the presence of H2A.Z-containing nucleosomes at gene promoters is inversely proportional to their transcription rates [29-31]. However, the opposite applies to human cells and *Drosophila* where H2A.Z shows a high degree of colocalization with Pol II [33, 34, 36] and is required for transactivation during hormone receptor signaling [37]. Yeast H2A.Z is thought to mark promoters that have undergone Pol II transcription initiation, as untranscribed genes do not contain Htz1. Since most genes in yeast are actively transcribed, this explains the wide-spread presence of Htz1 at most promoters.

Replacement of H2A by H2A.Z at nucleosomes is catalyzed by the Swr1 complex [38-40] and its metazoan orthologs SRCAP and p400 [41, 42] and requires prior acetylation of histones H3 and H4 [32, 43, 44]. The Ino80 chromatin remodeler mediates the reverse reaction, substituting H2A.Z with H2A [45].

3.3 Histone modifications

Histones are subject to a vast number of post-translational modifications (PTMs), such as methylation of arginine (R) residues; methylation, acetylation, ubiquitination, ADP-ribosylation and sumoylation of lysine (K) residues; and phosphorylation of serine (S) and threonine (T) residues (Fig. 1) (reviewed in [46]). Modification of histones are carried out by specialized enzymes, some of which display rather broad specificities such as the Gcn5 histone acetyltransferase, while yet others are known to modify single sites only, eg. the Set1

and Set2 lysine methyltransferases (KMTs) (Table 1). Certain modifications are generally associated with actively transcribed (euchromatin) or repressed chromatin (heterochromatin) states. Most modifications exhibit distinct spatial and/or temporal distributions and are associated with enhancers, promoters, open reading frames (ORFs), differentiation states or cell-cycle stages (Fig. 2). Histone modifications by themselves can alter the charge distribution and DNA contacts with histone octamers, thus influencing chromatin structure directly. Most prominently, acetylation of histone H4K16 has been shown to directly prevent folding of chromatin into higher-order structures [47]. Furthermore, histone modifications also serve to recruit downstream effectors that influence chromatin structure. A number of domains have been identified that can interact specifically with modified histones (Table 1) (reviewed in [48, 49]).

3.4 Histone modifications and transcription

Histone modification states associated with both silenced chromatin as well as active genes have been characterized in great detail over the last few years. In the section below we aim to focus particularly on histone modifications associated with transcriptionally active chromatin (Fig.2).

3.4.1 Histone acetylation—Newly synthesized histone H4 is acetylated at K5 and K12, while soluble histone H3 is modified at K56 [50, 51]. These marks are important for their deposition and are quickly removed following incorporation into chromatin. A second group of HATs acetylates histones at multiple sites in a chromatin-specific context (reviewed in [52]).

Histone acetylation disrupts the electrostatic interactions existing between the positively charged histones and the negatively charged DNA by neutralizing the positive charges of lysine residues [53, 54]. Thus it is not surprising that, taken as a group, acetylation correlates with transcription activation (Table 1). Acetylated lysines are generally recognized by bromodomains that are found in a large number of other factors, eg. the RSC and SWI/SNF remodeling complexes (reviewed in [49]).

3.4.2 Histone H3K4 methylation and H2B monoubiquitination—Methylation of H3K4 in yeast is carried out by a single methyltransferase, the Set1 complex (COMPASS) within a pathway highly conserved from yeast to humans [55, 56]. In comparison, *Drosophila* have three H3K4 methylase complexes, namely Trithorax (Trx), Trithorax-related (Trr) and dSet1. Mammals contain at least six such complexes: SET1A, SET1B, as well as MLL1- 4. SET1A and SET1B are orthologs of dSet1; MLL1 and MLL2 are related to Trx, while MLL3 and MLL4 derived from Trr (reviewed in [57]). All COMPASS-like complexes are built around the catalytic Set1 or MLL protein and core subunits Cps60/ASH2, Cps30/WDR5 and Cps50/RBBP5, in addition to several complex-specific subunits [57]. H3K4 monomethylation only requires a core complex consisting of Set1, Cps30 (Swd3) and Cps50 (Swd1). Di- and trimethylation of H3K4 by Set1/COMPASS is a highly regulated process that depends on prior monoubiquitination of H2B on Lys123 (H2Bub) by the Rad6/Bre1 E2/E3 ubiquitin ligase complex [58, 59]. H2B ubiquitination itself is the product of a complex regulatory cascade for which Pol II functions as a central recruitment

platform. H2Bub requires active Pol II transcription as shown by its dependence on the activity of Kin28, a Pol II Ser5-specific CTD kinase that marks the transition from Pol II initiation to elongation [60]. Transcribing Pol II stimulates recruitment of the PAF complex through its association with phosphorylated elongation factor Spt5 [61, 62]. PAF in turn associates with the Rad6/Bre1 ubiquitin ligase. Both Spt5 and Rad6 are regulated by the Bur1/Bur2 protein kinase complex, which further links PAF binding and H2B ubiquitination. H2Bub is recognized by COMPASS component Cps35 (Swd2), which then recruits the other COMPASS subunits to enable H3K4 di- and trimethylation (reviewed in [57]). Methylation of H3K4 requires H2B ubiquitination, but not vice versa, as the levels of H2Bub are not affected in an H3K4R site mutant that cannot be methylated and therefore mimics an unmodified lysine residue.

In flies and mammals dSet1 and SET1A/B are the primary H3K4 di- and trimethylase complexes, respectively. Analogous to yeast, they also rely on the PAF complex and H2B ubiquitination (though on K120 rather than K123) for H3K4 trimethylation [57]. Interestingly, the *C. elegans* ortholog of dSet1 plays a role in the regulation of life span, as lower levels of H3K4 methylation have been linked to extended life spans [57]. Whether this process depends on H2B ubiquitination and/or H3K4 di- and trimethylation remains to be seen.

The MLL complexes lack the ortholog of yeast Cps35 (mammalian WDR82) and are likely recruited independently of H2Bub. Instead, they function as transcriptional coactivators, involved in processes such as activation of the developmentally important *Hox* genes or nuclear receptor transactivation (reviewed in [57]). Misregulation of any of these complexes can have serious consequences: chromosomal translocations of the *MLL1* gene are associated with acute myeloid and lymphoid leukemia, while mutations in *MLL4* have been linked to non-Hodgkin's lymphoma [57].

Trimethylated H3K4 is a hallmark of active promoters and the 5′ ends of ORFs and correlates well with increased levels of gene expression [63]. H3K4me2 is found throughout coding regions, while H3K4me1 localizes mostly towards the 3′ ends of ORFs [64].

In higher eukaryotes H3K4 monomethylation has also become a reliable indicator of gene enhancers [65, 66]. Furthermore, promoters of developmentally important genes in mammalian stem cells are marked by both H3K4me3 as well as H3K27 trimethylation (a repressive modification). Such “bivalency” is critical for proper gene regulation and stem cell commitment during differentiation (reviewed in [57]). However, we have yet to define the COMPASS-like complex(es) involved in the regulation of H3K4 methylation of either phenomenon.

H3K4 methylation does not affect either elongation rate or processivity of Pol II by itself [67]. Rather it functions as a signaling platform that is recognized by a host of other factors through recognition modules that may specifically recognize a single modification state or exhibit somewhat broader specificity. Thus, unmethylated H3K4 recruits proteins through their PHD, WD40 or ADD domains. Many more proteins are known to bind to methylated H3K4 through PHD, Chromo, Tudor, MBT and Zf-CW domains (reviewed in [48]). Proteins

recruited through H3K4 methylation fulfill a number of different functions: many have been shown to be involved in chromatin remodeling and histone modification and play important roles during transcription, such as the human CHD1 and BPTF ATPases, or Sgf29 and Yng1 which are part of the yeast SAGA and NuA3 HATs, respectively [68-72]. However, other proteins involved in diverse processes such as DNA methylation (Dnmt3L) or recombination (RAG2) are also recruited by H3K4 methylation [73, 74].

3.4.3 Histone H2B monoubiquitination—Monoubiquitination of histone H2B is a modification found both at promoters and over open reading frames [60, 75-78] and has functions independent of its involvement in histone H3 lysine methylation. While incorporation of ubiquitin does not greatly affect nucleosome structure [79, 80], recent work shows that H2Bub prevents compaction of the chromatin fiber into a higher-order structure [81]. In this respect the effects of H2B ubiquitination are similar to those of H4K16 acetylation, although these two histone modifications function in parallel pathways [81]. Furthermore, H2B ubiquitination has been shown to promote reassembly of nucleosomes in the wake of elongating Pol II [76, 79, 82]. Reduced nucleosome occupancy was observed for an H2BK123A site mutant, whereby the most highly expressed genes showed the largest reductions in nucleosome occupancies [76]. Reassembly seems to involve the Chd1 remodeling enzyme, although it is currently not clear how this is achieved mechanistically [83]. Pol II elongation is further helped by increased DNA accessibility as a result of H2Bub-dependent stimulation of FACT activity [82, 84]. No bona fide ubiquitin-binding domain has been identified so far, although H2Bub is required for the binding of the COMPASS Cps35 subunit to chromatin [85].

3.4.4 Histone H3R2 methylation—Three modification states exist for arginine residues: monomethylation, symmetric dimethylation (Rme2s) and asymmetric dimethylation (Rme2a). Symmetric H3R2 methylation has only been observed in higher eukaryotes so far and is mediated by PRMT5 and PRMT7 [86]. In contrast, asymmetric H3R2 methylation exists in both yeast and metazoans, although the methyltransferase responsible, PRMT6, has only been identified in higher eukaryotes [87, 88].

The status of histone H3R2 methylation plays an important role for H3K4 methylation and thus for gene expression. Asymmetric H3R2me2 is mutually exclusive with trimethylated H3K4 and accumulates over mid- to 3′-regions of ORFs as well as over the promoters of inactive genes [87, 89]. In yeast, H3R2me2a abolishes binding of the COMPASS subunit Cps40 (Spp1) to mono- and dimethylated H3K4 through its PHD domain due to steric hindrance [89]. This interaction is however necessary for efficient H3K4 trimethylation [90]. Similarly, in humans presence of H3R2me2a inhibits binding of the MLL methyltransferase complex via the WD40 domain of its WDR5 subunit, with negative consequences for H3K4me3 [87, 88]. Vice versa, presence of the H3K4me3 mark also interferes with PRMT6-mediated methylation of H3R2 [87, 88].

Symmetric methylation of H3R2 has the opposite effects when compared to H3R2me2a. It is found at the −1 nucleosome of promoters as well as at promoter-distal sites [86]. H3R2me2s enhances binding of WDR5 which results in increased levels of H3K4me3. Conversely, depletion of H3R2me2s via knock-down of PRMT5 and PRMT7 also reduced H3K4me3

levels. Furthermore, the presence of H3R2me2s also blocked binding of RBBP7, a component of several co-repressor complexes such as the Sin3a histone deacetylase complex [86].

3.4.5 Histone H3K79 methylation—Methylation of H3K79 is mediated by Dot1 [91, 92] which preferentially methylates histone H3 in a nucleosomal context [93]. Similarly to H3K4, efficient trimethylation of H3K79 requires prior ubiquitination of histone H2B [94-96], which is thought to improve Dot1 processivity, possibly through allosteric changes [97-99]. Interestingly, H2Bub seems to stimulate Dot1-mediated H3K79 methylation both directly and indirectly: Dot1 directly binds ubiquitin [100], but it also associates indirectly with H2Bub through other proteins such as proteasomal ATPases Rpt4 and Rpt6 [101] or the Set1/COMPASS subunit Cps35 when overexpressed [85]. Currently, methylated H3K79 is the only histone methyl mark where no corresponding demethylase has been identified, although there are indications that H3K79 methylation can be reversed *in vivo* [102].

While we have a relatively good understanding of the role of H3K79 methylation in DNA damage response and cell cycle regulation, its link to transcription is less clear. In yeast, methylated H3K79 is depleted from telomeric, mating-type and ribosomal DNA, but ubiquitous everywhere else which accounts for ~90% of the yeast genome [63, 103]. Also, H3K79 methylation restricts recruitment of Sir proteins to heterochromatic regions and thus generally coincides with euchromatin [103]. H3K79 methylation is associated with transcribed genes in flies, mice and humans [104-106].

Several DOT1L-associated complexes have been identified in mammals that also contain the Pol II Ser2-specific CTD kinase P-TEFb, thus further suggesting involvement of Dot1 in transcription elongation [107, 108]. Purification of the DOT1L-containing complex DotCom also pulled down members of the Wnt pathway. P-TEFb was not isolated with this particular complex. However, DOT1L was nevertheless required for the expression of Wingless target genes, thus further supporting its role in transcription activation [109]. Similarly, a recent paper also implicates DOT1L in the regulation of JAK-STAT-dependent genes [110]. In mice DOT1L-mediated H3K79 methylation directly regulates expression of *dystrophin*, leading to defects during cardiac development when mutated [111]. However, the mechanism linking H3K79 methylation to transcription activation and elongation remains unclear and requires further investigation. Only a single recognition module for methylated H3K79 has been identified: however, the Tudor domain of 53BP1 has been shown to be involved in DNA repair rather than transcription [112].

3.4.6 Histone H3K36 methylation—Methylation of H3K36 is a widespread histone modification associated with ORFs [63]. Methylation of H3K36 is mediated by Set2, the sole histone H3K36 methyltransferase in yeast [113, 114]. While mono-and dimethylation of H3K36 by the Set2 catalytic domain require no other factors, H3K36me3 is dependent on full-length Set2 and its association with Pol II [115]. In particular, phosphorylation of the Pol II CTD by Ctk1 on Ser2 specifically stimulates Set2 binding [116-119] and is thought to positively affect Set2 protein stability [120]. Ctk1 is required for proper H3K36 trimethylation [115, 117, 119], which accumulates towards the 3′ ends of ORFs [63] (Fig.

2). H3K36 methylation is also affected by the proline isomerase Fpr4, which acts on H3P38 and antagonizes H3K36me levels *in vivo* [121].

H3K36me2 and H3K36me3 are generally associated with actively transcribed genes, yet only H3K36me3 levels correlate with transcription rates [63, 122]. H3K36 methylation is associated with transcribed genes and hence usually referred to as an activating histone mark. However, it actually exerts a repressive effect on chromatin structure as H3K36 di- and trimethylation signal for the deacetylation of histones H3 and H4 in the wake of Pol II passage through activation of the Rpd3S histone deacetylase complex [123-125]. Methylated H3K36 can be read by a number of different recognition modules. Rpd3S contains a chromo-as well as a PHD domain on its Eaf3 and Rco1 subunits. While the Eaf3 chromodomain recognizes H3K36me3 specifically, it functions in combination with the Rco1 PHD domain to bind H3K36 methylated nucleosomes [123, 126]. An increasing number of PWWP-domain proteins also bind preferentially to H3K36 trimethylated nucleosomes, such as the BRPF1 subunit of human MOZ acetyltransferase, which together with H3K36me3 is important for *Hox* gene expression [127, 128]. Other examples include the chromatin-associated Psip1 short (p52) isoform which plays a role in alternative splicing [129] and the Ioc4 subunit of the yeast Isw1b chromatin remodeler [130, 131] which relies on H3K36 methylation to maintain ordered chromatin over transcribed ORFs (see below) [130].

In contrast to yeast, eight different H3K36 methyltransferases have been identified in higher eukaryotes so far: NSD1-3, SETD2/3, ASH1L, MES4, SETMAR and SMYD2 (reviewed in [132]). While *in vivo* substrate specificities have not been determined for all enzymes as yet, SETD2 is thought to be the only human methyltransferase mediating H3K36 trimethylation in cells [133]. SETD2 is also the closest ortholog of yeast Set2 and interacts with Pol II during transcription elongation [134]. All other enzymes seem to be mono- and dimethylases. Some also act on other histone as well as non-histone targets: NSD1, for example has been reported to methylate NFκB as well as histone H4K20 [132]. NSD2 methylates H3K36 in a nucleosomal context, but prefers H4K44 when confronted with histone octamers. NSD2 is an interesting enzyme, as addition of short DNA molecules that may function as allosteric effectors, results in subsequent preferential H3K36 dimethylation of histone octamers [135]. The higher complexity of H3K36 methylases in humans also suggests more wide-spread biological involvement when compared to yeast. Indeed, in metazoans H3K36 methylation has been implicated in a number of processes, including gene activation and repression, alternative splicing, dosage compensation, as well as DNA replication, recombination and repair [132]. At the same time, dysfunctional H3K36 methylation has been linked to a large number of diseases, including for example severe developmental defects, breast, lung and prostate cancer, acute myeloid leukaemia, and neuroblastoma (reviewed in [132]). Efforts to elucidate the mechanisms governing these processes are still in the beginning stages.

4. Maintenance of genome integrity

Chromatin represents a barrier for efficient Pol II transcription, which is alleviated by the action of a number of positive transcription elongation factors. At the same time chromatin

structure needs to be restored in the wake of Pol II passage. Failure to do so leads to gross perturbations in the nucleosomal organization of genes and exposure of intragenic (cryptic) promoter-like sequences that initiate aberrant transcription from inside open reading frames (Text box 1) [136].

Text box 1 What is cryptic transcription?

The term “cryptic” transcription is used to refer to two different, yet overlapping processes. It was first used to describe the presence of transcripts initiated from intragenic promoters that are usually inaccessible for assembly of the transcription machinery [136]. Transcription from these promoters may occur in either the sense or antisense direction, and sometimes in both [137, 138]. Furthermore, intragenic promoters can be found anywhere over ORFs and are not necessarily associated with the nucleosome-free regions of genes (see below). RNAs produced from cryptic promoters are stable and often, but not always polyadenylated, as cryptic transcripts have been identified from mRNA as well as total RNA fractions. Also, the Winston lab has shown that at least some of these intragenic transcripts are translated into proteins [137], although whether these protein products have any functional roles remains to be determined.

More recently a lot of attention has been focused on the wide-spread, “pervasive” transcription of non-coding RNAs (ncRNA), that are also often referred to as cryptic transcripts (reviewed in [139, 140]). For the purposes of this review we will refer to the intragenic transcripts described above as “cryptic” and to all others as “pervasive”. Generally these pervasive ncRNAs are further categorized as cryptic unstable transcripts (CUTs) or stable unannotated transcripts (SUTs). SUTs can be identified in wildtype yeast [141, 142], whereas CUTs are observed in yeast strains with impaired RNA degradation pathways, such as the exosome mutant *rrp6*Δ [143]. More recently, a third group of ncRNAs has been identified that relies on the Xrn1 5′-3′ RNA exonuclease for degradation and is therefore named Xrn1-sensitive unstable transcripts (XUTs) [144]. There is a certain amount of overlap between these groups as ~ 30% of SUTs and ~ 10% of CUTs are also XUTs [144]. Presumably, this also applies to the intragenic cryptic transcripts, as we have no information as to the regulation of their degradation.

CUTs, SUTs and XUTs are polyadenylated transcripts. They are generally initiated from nucleosome-free regions at either the promoter or the 3′ intergenic region and transcription occurs mostly from the antisense strand [141, 144]. In the case of divergent CUTs transcribed in both the sense and antisense direction, expression of sense CUTs correlates negatively with gene transcription rates, whereas the reverse is true for antisense CUTs, suggesting a mechanism of transcriptional interference with normal gene expression [141, 142]. A recent study found, however, that in yeast transcription is highly directional and favors the sense orientation. This preference is dependent on functional Rpd3S histone deacetylase [145].

Determining the functional significance of these ncRNAs is an ongoing focus of research, but a regulatory role in gene expression has been identified for a number of ncRNAs. For example, *PHO84* antisense transcripts inhibit sense transcription of the *PHO84* gene both *in cis* and *in trans* [146, 147]. In both instances silencing of *PHO84* requires production of the

antisense transcript. However, *cis* inhibition relies on the Hda1/2/3 histone deacetylase which leads to promoter deacetylation [146]. In contrast, *trans* silencing requires functional Set1 as increased H3K4 trimethylation promotes production of the antisense transcript [147]. Pervasive transcription has also been identified in higher eukaryotes (reviewed in [139, 140]), eg. the human *HOTAIR* transcript that is involved in the silencing of the *HOXD* locus *in trans* through interactions with PRC2 [148]. While most known examples of ncRNAs are linked to repression, several ncRNAs promote gene expression. The *Drosophila* roX RNAs mark the male X chromosome and cooperate with the MSL complex to enhance transcription elongation over genes involved in male dosage compensation [149]. Another example is *HOTTIP* which directly binds to the WDR5 subunit of MLL H3K4 methylases to activate transcription of *HOXA in cis* and results in increased levels of H3K4me3[150].

4.1 Properties of cryptic promoters

Cryptic promoters are diverse and do not fall into a single group. Some, such as the promoter present within the *FLO8* gene contain a TATA-box while others, eg. at the *STE11* locus do not [136, 151]. Recent work has shown that cryptic promoters are regulated independently from their respective canonical promoter [151]. Furthermore, transcription initiation from cryptic promoters relies on the same components of the transcriptional machinery as their canonical counterparts [151]. It may be expected that transcription from cryptic promoters interferes with the production of the corresponding full-length transcripts. However, several gene expression microarray experiments of mutants with known cryptic transcript phenotypes did not exhibit large-scale changes in overall gene expression and therefore argue against this idea [130, 137, 138, 152, 153]. This may be explained by the observation that cryptic transcript genes tend to be infrequently transcribed [137, 138].

4.2 Histone chaperones

The Winston laboratory used a genetic screen to systematically identify genes required for the repression of cryptic transcription. In agreement with the data published from a number of laboratories, the strongest phenotypes were associated with mutations in histones, regulators of histone genes, transcription elongation factors, histone chaperones, chromatin remodelers and histone modifiers [137, 154]. These observations argue that any mutation that results in reduced nucleosome occupancy and increased DNA accessibility results in the production of cryptic transcripts (Fig. 3). Indeed, aberrant intragenic transcription was first identified in mutants of the Spt6 and Spt16 (FACT) histone chaperones, known to play a role in nucleosome reassembly during transcription elongation [136, 155, 156]. Similar findings were also obtained for a Rtt106-deficient strain: Rtt106 is a histone chaperone associated with coding sequences and involved in histone H3 deposition over ORFs [154, 157]. Furthermore, the cryptic transcript phenotype of a *rtt106*Δ strain was exacerbated by the additional mutation of *SPT6* [157].

4.3 Set2-Rpd3S pathway

Deletion of components involved in the Set2-Rpd3S pathway such as Set2 or Rco1 exhibit the same phenotype [123, 124]. Either mutation results in the generation of hyperacetylated chromatin over open reading frames which is thought to adopt a less compact structure and thus allow for intragenic transcription initiation.Similarly, mutation of key residues in

histones H4 (K44), H2A (L116, L117) and H3 thought to interfere with nucleosome binding by Set2 result in lower levels of H3K36 di- and trimethylation, increased levels of histone H4 acetylation and the appearance of cryptic transcripts [158-160] (Fig. 3B). Deletion of Ctk1, a kinase that specifically phosphorylates Ser2 of the Pol II CTD and vital for recruitment of Set2 to elongating Pol II also causes a severe cryptic transcript phenotype due to a complete lack of di- and trimethylated H3K36 in this mutant [137].

Recent work from our laboratory has shown that H3K36 methylation plays a more fundamental role in preserving chromatin architecture than previously thought. We found that H3K36 methylation affects histone dynamics, as it prevents the incorporation of new, acetylated histones over transcribed ORFs and thereby promotes the retention of H3K36 methylated nucleosomes *in cis* (Fig. 3A) [153]. Furthermore, increased histone exchange over ORFs seems to be responsible for the bulk of histone hyperacetylation in a *SET2* mutant, suggesting that higher histone turnover contributes significantly to the increased acessibility of cryptic promoters (Fig. 3B) [153].

Retention of H3K36-methylated nucleosomes over ORFs relies on chromatin remodelers Isw1b and Chd1. Deletion of these remodelers results in increased histone turnover, histone acetylation and wide-spread cryptic transcription, while having no or little effect on H3K36 methylation levels (Fig.3C) [130, 161]. Both remodelers act within the Set2 pathway as deletion of either in a *set2*Δ background shows similar levels of cryptic transcription and histone acetylation when compared to a *set2*Δ single deletion [130]. Isw1b is recruited directly by H3K36 methylated nucleosomes *in vivo* and *in vitro* [130, 131]. Chd1 has not been shown to interact preferentially with H3K36 methylated nucleosomes [162, 163], but it is known to bind to several transcription elongation factors such as the PAF complex and Spt5 [164] and thus may be brought in by Pol II itself.

Suppression of cryptic initiation by H3K36 trimethylation has also been observed in higher eukaryotes. Self-renewal of embryonic stem cells (ESCs) is partly regulated through control of histone methylation. The H3K4me3-specific demethylase KDM5B (JARID1B) is recruited to intragenic regions by interaction of its chromodomain protein MRG15 with trimethylated H3K36 nucleosomes [165]. KDM5B is important for maintaining low levels of H3K4 trimethylation over ORFs, as knock-down of either KDM5B or MRG15 results in marked increases of H3K4me3, recruitment of non-phosphorylated Pol II and increased cryptic transcription [165]. KDM5B also interacts with the Rpd3S orthologs HDAC1 and Sin3A, providing a further link to the Set2-Rpd3 pathway. In contrast to yeast, increased cryptic transcription in ES cells concurrently reduced levels of the functional full-length mRNA [165] .

4.4 Cryptic transcription and H2Bub

Other mutations known to cause cryptic transcription are *bur2*Δ and deletion of the PAF complex subunit Ctr9. Both are elongation factors known to play roles in histone H2B ubiquitination and early transcription elongation [166, 167]. Interestingly, mutations in both *BUR2* and the PAF complex result in significant reductions of H3K36 tri- but not dimethylation [168]. While dimethylated H3K36 is sufficient to prevent cryptic transcription [162], deletion of *BUR2* or *PAF1* exhibited additive effects on cryptic transcription in a

*set2*Δ background when compared to *set2*Δ alone. These results suggest that Bur2 and the PAF complex do not act within the Set2 pathway, but act in parallel with Set2 [168].

A recent study on the effects of H2Bub on chromatin organization concluded that the presence of H2Bub stabilizes nucleosomes. Furthermore, yeast strains with a histone H2BK123A mutation or deletion in the gene encoding the ubiquitin-conjugating enzyme Rad6 displayed reduced levels of histone H3 over coding regions genome-wide [76]. These results suggest that in both *bur2*Δ and *ctr9*Δ strains cryptic transcription may be a consequence of increased nucleosomal disassembly and/or decreased reassembly in the wake of Pol II passage, analogous to histone chaperone defects. In agreement with these data, cryptic transcription has been reported for strains with a histone H2BK123R mutation or deletions in the H2B ubiquitination pathway (*rad6*Δ, *bre1*Δ, *lge1*Δ) [82, 154], although another report did not detect cryptic transcripts for either *bre1*Δ or *lge1*Δ [162]. This discrepancy is presumably accounted for by different experimental approaches.

Chd1 was recently shown to play a role in the maintenance of H2Bub levels over coding regions [83], which indicates that it may be part of the same pathway (Fig. 3D). However, it is worthwhile to point out that deposition of H2Bub and H3K36me3 marks over ORFs is highly correlated, as both are enriched over long and highly transcribed genes [77]. Chd1 prevents histone exchange in yeast [130, 161]. Furthermore, *Drosophila* CHD1 can catalyze the transfer of histones from the histone chaperone NAP1 onto DNA *in vitro* [16] and it is also important for the replication-independent deposition of histone variant H3.3 in male fly pronuclei [169]. Taken together, these results suggest that nucleosomal reassembly may be impaired in a *chd1*Δ mutant. Genome-wide ChIP-seq experiments observed relatively small reductions in positioned nucleosomes over ORFs [83, 152], but ChIP-chip data show a clear redistribution of nucleosome occupancy from the 3′- towards the 5′-end of ORFs [130]. The mechanism by which Chd1 affects the initiation of cryptic transcription is not entirely clear at this time. Given the fact that a *chd1*Δ strain also exhibits a weak cryptic transcript phenotype [130, 137, 163] and seems to be involved in the Set2 pathway, it will be interesting to determine its contribution to the H2Bub pathway.

5. Future directions

Our knowledge about histone modifications and how they are established, recognized and reversed has exploded over the last decade. Yet a number of enzymes have remained elusive. How recognition of histone modifications by downstream effector molecules is influenced by other, co-existing modifications will remain an interesting area of study, especially in higher eukaryotes where several histone modifiers and remodelers often tend to be part of the same complexes.

Cryptic promoters are common throughout the yeast genome. A small number are expressed even in wildtype cells. The question remains what function they serve, especially since we know that some at least are translated into proteins. Some cryptic transcripts are present in wildtype yeast in response to stress conditions [137] although their function remains elusive. Furthermore, aberrant intragenic transcription in yeast shares some similarities with the production of alternatively spliced transcripts found in higher eukaryotes. Nucleosomal

organization and H3K36 methylation play important roles in the regulation of alternative splicing. Interestingly, highly constitutive exons display higher levels of nucleosome occupancy and H3K36me3than alternative ones (reviewed in [170]). While H3K36 trimethylation is not the only histone modification to affect splicing, it may also regulate histone dynamics in metazoans and thus presumably impact alternative splicing. If so, it will be interesting to learn if lessons from yeast will be applicable.

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Highlights

- Histone modifications influence chromatin organization during transcription elongation.
- Histone chaperones and H2B ubiquitination maintain nucleosome levels over gene bodies.
- Disruption of histone H3K36 methylation leads to increased histone exchange and altered, hyperacetylated chromatin.
- Perturbation of chromatin structure over gene bodies exposes cryptic promoters.
- Cryptic transcripts are polyadenylated and even translated - their function is unclear though.

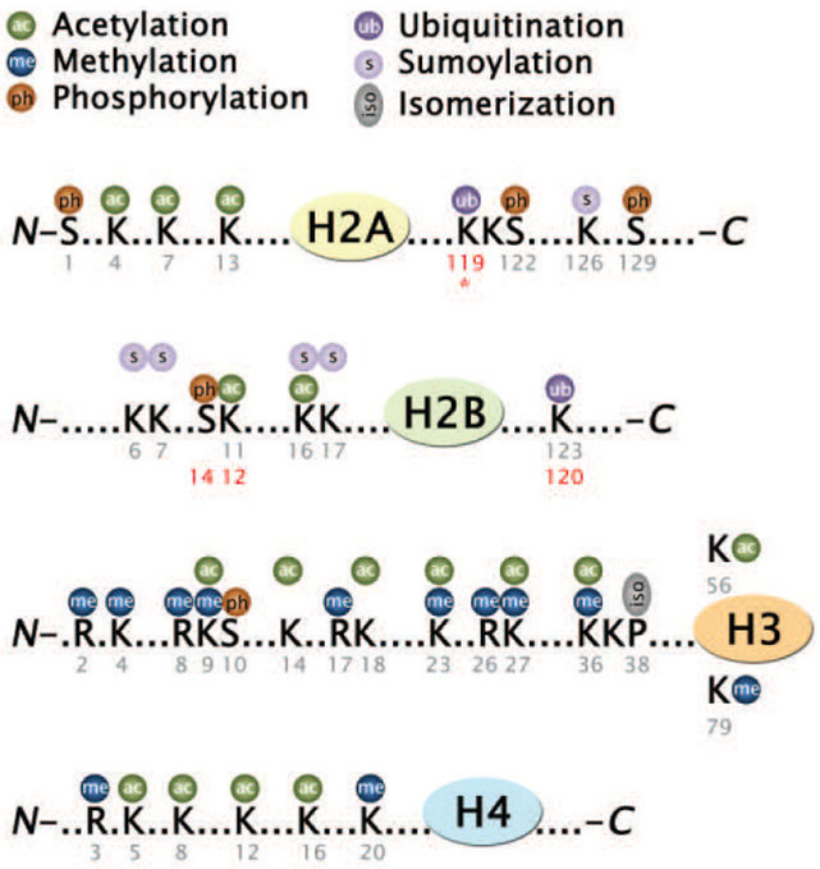

Figure 1.

Posttranslational modifications associated with yeast histones. Alternative residue numbers that refer to mammalian histones are shown in red. Ubiquitination of histone H2A on K119 does not exist in yeast (*).

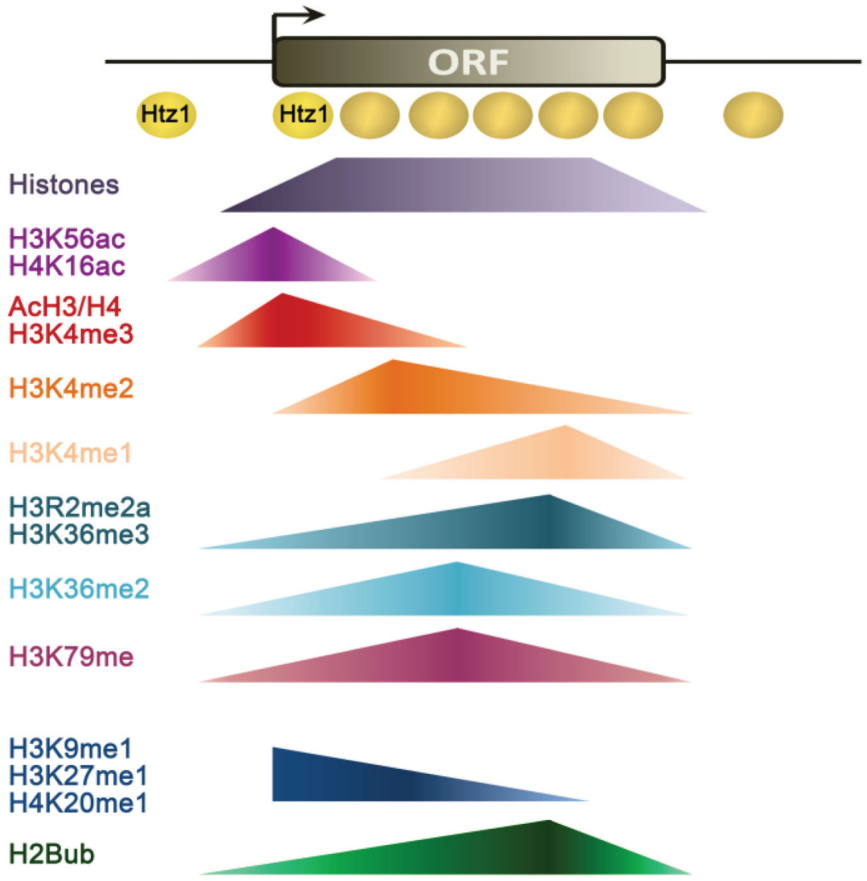

Figure 2.

Genome-wide distribution patterns of histone modifications involved in transcription. Distributions are shown relative to an average yeast gene: the promoter, transcription start site (arrow), coding sequence (ORF) and 3′ intergenic region are shown. All data sets refer to yeast with the exception of H3K9, H3K27 and H4K20 methylation.

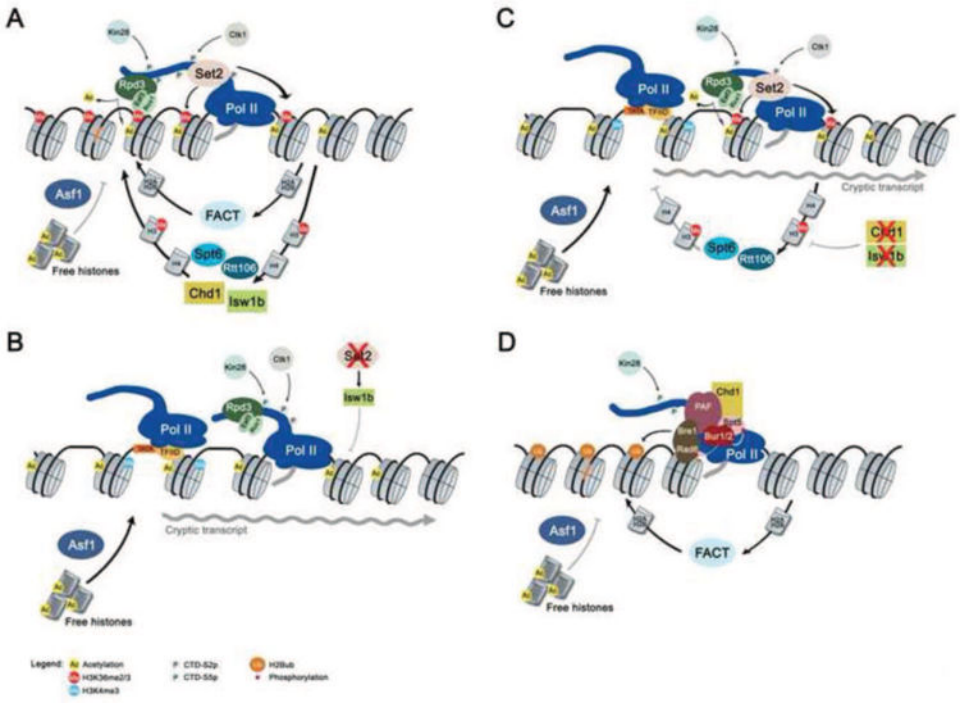

Figure 3.

Perturbation of chromatin structure leads to aberrant intragenic transcription. **(A)** Histone chaperones like FACT, Spt6 and Rtt106 aid transcription elongation by disassembly of nucleosomes in front of Pol II and subsequent reassembly in its wake. Kin28 and Ctk1 specifically phosphorylate Ser5 and Ser2 within the CTD heptad repeats, respectively. Set2 is recruited to the elongating polymerase through the Ser2 phosphorylated form of the CTD and methylates Lys36 on histone H3. Methylated H3K36 recruits chromatin remodelers such as Isw1b and ensures the retention of these nucleosomes over ORFs . Maintaining H3K36 methylated nucleosomes disfavours incorporation of free, acetylated histones in their stead. Any remaining histone acetylation is removed by the Rpd3S histone deacetylase. Rpd3S associates with the Ser5 phosphorylated form of the Pol II CTD and recognizes methylated H3K36 through the chromo- and PHD-domains of its Eaf3 and Rco1 subunits, respectively. H3K36 di- and trimethylation stimulates Rpd3S activity and hence the removal of acetyl marks from transcribed chromatin [171]. **(B)** Mutations in key proteins involved in this pathway lead to perturbations in chromatin structure. Deletion of *SET2* completely abolishes H3K36 methylation and simultaneously allows for the incorporation of free, acetylated histones. Rpd3S is still recruited to ORFs through its association with Pol II. However, in the absence of H3K36 methylation it can no longer catalyze the removal of acetyl marks from histones H3 and H4. Alterations in the chromatin architecture and increased exposure of internal promoter-like sites lead to PIC formation and initiation of cryptic transcription from inside of open reading frames. **(C)** Absence of chromatin remodelers Isw1b and/or Chd1impairs the retention of H3K36-methylated nucleosomes *in cis* and leads to increased incorporation of free, acetylated histones over ORFs despite continued Set2 and Rpd3S activities. The resulting alterations in chromatin structure lead to PIC formation and cryptic transcription. **(D)** H2Bub exerts a stabilizing influence on nucleosomes. Establishment

requires a complex cascade of factors: H2Bub requires active Pol II transcription as shown by its dependence on Ser5 CTD phosphorylation by Kin28. Transcribing Pol II further stimulates recruitment of the PAF complex through its association with phosphorylated Spt5 [61, 62]. PAF in turn associates with the Rad6/Bre1 ubiquitin ligase. Both Spt5 and Rad6 are also regulated by the Bur1/Bur2 protein kinase complex, further linking PAF binding and H2B ubiquitination. Chd1 may also be involved in this pathway since it is known to interact both with PAF and Spt5 [164]. Disruption of this cascade is envisaged to result in lower levels of H2Bub over ORFs and consequently reduced nucleosome occupancy which is thought to expose cryptic promoters.

Table 1

Common histone modifications. Alternative residue numbers that refer to mammalian histones are shown in red. Enzymes known to mediate as well as remove any given modification are shown for *Saccharomyces cerevisiae* (*S.c.*), *Drosophila melanogaster* (*D.m.*) and their mammalian counterparts. Recognition modules that bind specific modifications are also indicated. If interaction partners but no specific domain(s) were identified, then the proteins are shown in brackets.

PTM	Position	Enzyme			Function	Recognized by	Reversed by		
		S.c.	***D.m.***	**Mammals**			***S.c.***	***D.m.***	**Mammals**
Lys Acetylation	H2AK4 K5	Esa1 [172]	Tip60 [173]	TIP60, P300/CBP, HAT1 [174-176]	Transcription activation		Rpd3 [177]		
	H2AK7	Esa1 [172]							
	H2BK11 K12	Gcn5 [178]		P300/CBP, ATF2 [175, 179]	Transcription activation		Rpd3, Hda1 [177]		
	H2BK16 K15	Gcn5, Esa1 [178]		P300/CBP, ATF2 [175, 179]					
	H3K9	Gcn5, Rtt109 [180, 181]	dGcn5 [182]	SRC1, PCAF [175, 183]	Transcription activation		Rpd3, Set3, Hda1, Hos2, Hst1 [177, 184]	dHDAC1 [185]	SIRT1/6 [186]
	H3K14	Gcn5, Hpa2, Esa1, Elp3, Sas2, Sas3 [172, 178, 180, 187-190]	dGcn5, Taf1, dCBP [182, 191]	P300/CBP, TAF1, hGCN5, PCAF, MOZ, MORF, TIP60, SRC1, HBO1 [174, 175, 183, 191, 192]		Bromo, PHD [193, 194]			
	H3K18	Gcn5 [180]	dCBP	P300/CBP [175, 195]					
	H3K23	Gcn5, Sas3 [178, 190]		P300/CBP [175]					
	H3K27	Gcn5, Rtt109 [178, 196]	dCBP [197]						
	H3K36	Gcn5 [198]							
	H3K56	Rtt109 [51]	dCBP [199]	P300/CBP [199]		PH, (Snf5) [200, 201]	Hst3/4 [202]	Sir2 [199]	SIRT1/2/6 [199, 203]
	H4K5	Esa1	Hat1, dCBP	HAT1, TIP60, P300, HBO1 [174, 204]	Transcription activation	Bromo [205]	Rpd3, Set3, Hos2, Hst1 [177, 184, 206]		
	H4K8	Esa1, Elp3, Gcn5 [188]	dCBP	TIP60, P300, HBO1 [174, 204]		Bromo [205]			
	H4K12	Hat1, Esa1, Hpa2 [187]		TIP60, P300, HBO1 [174, 204]					
	H4K16	Sas2, Esa1 [172, 189]	Mof, Atac2 [207, 208]	hMOF, TIP60, ATF2 [174, 179, 209]		Bromo [210]	Sir2 [211]	Sir2 [199]	SIRT1/2 [186, 212]
Lys Methylation	H3K4	Set1 [55]	Trx, Trr, Ash1, Set1 [213-216]	SET1, NSD2-3, SET7/9, MLL1-4, SMYD3, ASH1L [217-220]	Transcription activation	PHD, Chromo, WD40, ADD, Tudor, MBT, Zf-	Jhd2 [226]	Lid, Su(var)3-3 [227, 228]	LSD1, AOF1, JARID1A-D [229-231]

PTM	Position	Enzyme			Function	Recognized by	Reversed by		
		S.c.	*D.m.*	Mammals			*S.c.*	*D.m.*	Mammals
						CW [68, 73, 74, 221-225]			
	H3K9		Su(var)3-9, Ash1, G9a [215, 232, 233]	SUV39H1/2, G9a, Eu-HMT1, SETDB1, RIZ1, ASH1 [232, 234-237]	Silencing	PHD, Chromo, Tudor, WD40, Ankyrin [223, 238-241]	Rph1 [242]	dKDM4B [243]	LSD1, JHDM2A/B, JMJD2A-D, KIAA1718, PHF8 [244-248]
	H3K23					Chromo [249]			
	H3K27		E(z) [250]	EZH1/2, NSD2-3, G9a [217, 234, 251]	Silencing	Chromo, WD40 [240, 252]			
	H3K36	Set2 [113]	Set2, Mes4, Ash1 [253-255]	SETD2-3, NSD1-3, SMYD2, ASH1L, SETMAR [254, 256-258]	Transcription elongation	Chromo, PHD, PWWP [128, 259, 260]	Jhd1, Rph1, Gis1 [242, 261, 262]	dKDM4A/B [243]	JHDM1A/B, JMJD2A-C [246, 263]
	H3K79	Dot1 [92]	Grappa [109]	DOT1L [93]		Tudor [112]			
	H4K20		Pr-set7, Suv4-20, Ash1 [215, 264-266]	ASH1L, NSD1, Pr-SET7, SUV4-20H, NSD2 [257, 264, 265, 267, 268]	Transcription activation/ repression	Tudor, MBT, PWWP, WD40 [70, 224, 269]			KIAA1718, PHF8 [247, 248]
Arg Methylation	H3R2me2a me2s	? [270]		PRMT6 PRMT5/7 [86, 271]	Transcription repression/ activation	WD40 [86]			JMJD6 [272]
	H3R8			PRMT5 [273]	Transcription repression				PAD4 [274]
	H3R17			CARM1 [195]	Transcription activation	Tudor [275]			PAD4 [274]
	H3R26			CARM1 [276]					
	H4R3	Rmt1 [91]		PRMT1, PRMT5 [273, 277]	Transcription activation	Tudor, ADD, (p300/PCAF) [275, 278, 279]			JMJD6, PAD4 [272, 274]
Phos	H2BS10 S14	Ste20 [280]		MST1 [281]	Apopotosis				
	H3S10	Snf1, Ipl1 [282, 283]	Jil1, Aurora B [284, 285]	MSK1/2, IKKα, PKB, RSK2, PIM1, Aurora B, JNK[286-291]	Transcription activation, mitosis, meiosis	(Gcn5), 14-3-3 [292, 293]	Glc7 [283]	PP2A [294]	
Ub	H2AK119		Ring1B [295]	Ring1B, 2A-HUB [296, 297]	Transcription repression			Calypso [298]	USP3, USP16, USP21, USP22, 2A-DUB [299-303]
	H2BK123 K120	Rad6, Bre1 [58, 304]	Rad6, Bre1 [305, 306]	HR6A/B, RNF20/40, UbcH6 [307, 308]	Transcription activation	(Cps35) [85]	Ubp8, Ubp10 [309, 310]	Nonstop,Scrawny,USP7[311-313]	USP3, USP22 [299, 314]
Sumo	H2AK126	Ubc9, Siz1, Siz2 [315]			Transcription repression				
	H2BK6/7								
	H2BK16/K17								

PTM	Position	Enzyme			Function	Recognized by	Reversed by		
		S.c.	*D.m.*	Mammals			*S.c.*	*D.m.*	Mammals
	H4K5 K8 K12 K16 K20	Ubc9, Siz1, Siz2 [315]		UBC9					