In eukaryotes, genomic DNA is hierarchically packaged into chromatin by histones. A defined organization of the genome into chromatin with specific patterns of epigenetic modifications is crucial for transcriptional regulation, cell fate determination, and maintenance, in which the histone variant incorporation has been characterized as one of the most key players. The diversity of histone variants results in structural plasticity of chromatin and highlights functionally distinct chromosomal domains. Here we focus on the role of histone variant H3.3 and its coregulation with H2A.Z in chromatin dynamics at enhancers and promoters and transcriptional regulation.

Introduction

The accessibility of genomic DNA in eukaryotes is believed to be highly regulated by chromatin dynamics. Establishment of a proper chromatin landscape is critically important for genome function and integrity. The cell-type specific pattern of gene expression is characterized not only by the primary genomic DNA sequence but also by the distinct spatial organization of genome into chromatin with distinct structures that are modified by epigenetic factors including DNA methylations, histone variants and/or modifications, and other chromatin binding factors. In particular, the chromatin dynamics around the promoter and enhancer regions—which are highly regulated to accommodate binding of transcriptional factors and RNA polymerases machineries during the process of gene transcription—are of critical importance. Besides the bulk packaging role of canonical histones, different histone variants have evolved distinct regulatory mechanisms for their expression, deposition, and functional implications in chromatin dynamics and transcriptional activities. Recent studies have demonstrated that two major histone variants, H3.3 and H2A.Z, are highly enriched at these regulatory regions and involved in transcriptional regulations. It is of great interest to investigate how the variants are incorporated into regions of genome, how they decorate specific chromatin states for gene regulation, and how they are involved in cell fate determination and maintenance. In this review we focus on the recent studies of epigenetic regulation and functional implications of the histone variant H3.3 and its coregulation with H2A.Z at enhancers and promoters.

Histone Variant H3.3 vs. Canonical H3

The histone variant H3.3 is one of the most conserved variants in all eukaryotes. In most metazoans, H3.3 displays only four amino acid differences compared with canonical H3, including residue 31 (Ser vs. Ala) in the N-terminal tail and residues 87 (Ala vs. Ser), 89 (Ile vs. Val), and 90 (Gly vs. Met) near the
beginning of α2 helix. The canonical H3 protein is encoded by a gene cluster with more than a dozen genes, expressed in S phase and incorporated into chromatin during DNA replication by its chaperone CAF-1—where H3.3 protein, encoded by two distinct genes H3F3a and H3F3b, is expressed throughout the whole cell cycle and deposited into distinct chromatin regions in a DNA replication-independent manner by different mechanisms. 10 Histone variant H3.3 has been largely considered as a marker of transcriptionally active genes but also involved in the formation of telomere and pericentric heterochromatin in mouse embryonic stem (mES) cells. 11,12 To date, a number of factors have been identified for proper incorporation of H3.3 at specific genomic regions: Different H3.3 chaperones are likely responsible for the deposition and localization of H3.3 at distinct genomic regions to accomplish different biological functions. The HIRA (HIR histone cell cycle regulation defective homolog A) complex has been found to account for the replication-independent assembly of H3.3 in transcribed chromatin regions. 10 It has been observed to physically associate with both initiation (Ser5 phosphorylation) and elongation (Ser2 phosphorylation) forms of RNA Pol II, which may account for the distinct H3.3 density profile in the highly transcribed genes; while the DNA binding ability of the HIRA complex without any sequence specificity may provide another potential nucleosome gap-filling mechanism for HIRA-dependent H3.3 deposition. 10 In contrast, DAXX (death-domain associated protein), another H3.3 specific chaperone, has been identified to be responsible for the deposition of H3.3 at telomeric heterochromatin in mES cells with the aid of ATRX (α-thalassemia X-linked mental retardation protein). 13,14 which has been shown to prefer sequences capable of forming G-quadruplexes and corresponded to the specific targeting of H3.3 to telomeres and pericentric heterochromatin. 15 However, the precise mechanisms of H3.3 incorporation remains obscure.

As mentioned above, H3.3 displays only several amino acid differences to canonical H3. How are these subtle differences translated into a loci-specific deposition of H3.3 with distinct functional properties? Recently, several mutational studies have been developed to specify the important roles of H3.3 specific residues in H3.3 deposition and function. The X-ray crystal structure of H3.3-H4 and DAXX revealed that the two H3.3 unique residues Ala87 and Gly90 are critical for the specific recognition of H3.3 by DAXX. 16-18 In Arabidopsis, the four unique amino acids have been shown to serve as a guide for the dynamic deposition of H3.3 in plant chromatin, in which H3.3 and Lys90 in the core domain guide nucleosome assembly, while Thr31 and Tyr41 in the N-terminal tail guide nucleosome disassembly in nucleolar (DNA). 19 In Drosophila, the Ala87, Ile89, and Gly90 residues has been shown to be necessary for replication-independent incorporation of H3.3 into nucleosomes. 16 Although a single mutation at the residue Ser31 in H3.3 results no effect on the deposition of H3.3, the specific residue Ser31 in H3.3 can be phosphorylated, which has been found to be enriched at the telomeres in mES cells and at pericentric heterochromatin in differentiated cells during mitosis. 20,21 But how these amino acid differences in H3.3 affect the properties of chromatin structures still remains to be addressed. Recently, we have conducted in vitro biophysical experiments to address this problem. 22 We found H3.3 greatly impairs higher-ordered chromatin folding, although it has no significant effect on the stability of mononucleosomes. Point-mutational analysis showed that all the four unique residues contribute to hinder the compaction of chromatin arrays. In addition, the incorporation of H3.3 can counteract the H2A.Z-mediated chromatin compaction, which is mainly caused by the two residues Ile89 and Gly90. Furthermore, H3.3 has also been found to counteract the association of the linker histone H1 in Drosophila; RNAi knockdown of H3.3 substantially increased the genomic binding of H1 and resulted an increase of nucleosome length. 22 The opening of higher-ordered chromatin structure caused by H3.3 incorporation may play an important role in connecting H3.3 with active transcription.

Dynamics of H3.3 at Enhancers and Promoters

In mammalian cells the nucleosomes present at promoters and enhancers are dynamically regulated to accommodate binding of transcriptional factors and RNA polymerases machineries during the process of gene transcription. The deposition of H3.3 by DAXX in these regions will critically impact the properties of nucleosomes and/or chromatin and regulate transcriptional activity. Genome-wide analysis has shown that H3.3 is largely enriched in the actively transcribed genes, transcriptional factor binding sites, and telomeres in mammalian cells. 5,20 Interestingly, our genomic analysis show that in mES cells the binding of H3.3 at enhancer regions is relatively higher than that at promoter regions, while the enrichment of H2A.Z is quite the reverse (Fig. 1A). Furthermore, enhancer regions are biected by H3.3 enrichment or not. The enhancers containing high level of H3.3 display lower level of H3K27ac and p300, and Pol II-Ser5p, which are mostly believed as “active enhancer” markers (Fig. 1B). Our result indicates that the enhancers enriched with H3.3 exhibit distinct features compared with that without H3.3 enrichment, which suggests that H3.3 might be an epigenetic marker for the “poised enhancer.” Consistently, a recent study has shown that in hela cells, H3.3 largely colocalizes with HIRA complex at poised enhancers, the regions enriched of H3K4me1 but lack of H3K27ac and p300. 26 Furthermore detailed analysis of the distribution of H3.3 at active and inactive genes has shown H3.3 enrichment at the promoters of transcribed gene but not of genes that are not expressed. 8,27 In addition, the investigation on the dynamic incorporation of H3.3 in mouse embryonic fibroblasts (MEFs) also revealed that the H3.3-containing nucleosomes at enhancers and promoters undergo rapid turnover, which may remain chromatin at an “immature” uncondensed state and keep DNA highly accessible at these regions. 28 However, how and when H3.3 incorporates into these regions and whether the deposition of H3.3 drives or just reflects the
transcriptional activity still remains to be elucidated. In order to address this problem, the dynamic incorporation of H3.3 and the related chromatin dynamics at regulatory elements during transcription activation have been investigated specifically for retinoid acid (RA)-induced genes.23 Time-course ChIP analysis revealed that the incorporation of H3.3 at the enhancers occurs in the resting stages of transcription and prior to gene induction, with low level of H3.3 at the promoter.23 In addition, EpiQ and genome-wide MNase-seq analysis demonstrated that the chromatin at enhancer regions enriched with H3.3 display a relative open conformation, which may facilitate the recognition and binding of transcriptional activators at this region.23 Knockdown of H3.3 resulted in chromatin compaction and impaired the subsequent binding of RAR, TBP, and Pol II on the enhancers and greatly inhibited gene expression during tRA induction.23 All the results indicated that the incorporation of H3.3 actively marks the enhancer region for gene activation. When the genes are activated by tRA, the H3.3-containing nucleosomes are rapidly displaced from enhancers; by contrast, the H3.3 is incorporated into the promoter regions in the meanwhile. The H3.3 deposition at the promoter is concomitant with gene activation. It is clear that the incorporation of H3.3 into enhancers and promoters occurs separately at different times during the process of transcription, but whether they are accomplished by different mechanisms still remains to be clear. It would also be interesting to investigate whether HIRA, DAXX, or other undetermined H3.3 specific chaperones account for these two different dynamic processes of H3.3 at enhancers and promoters during gene activation.

Coregulation of H2A.Z with H3.3 in Gene Transcription

The variant H2A.Z has been implicated in a wide range of DNA-mediated processes including transcription, DNA repair, and genomic stability. Numerous studies have shown that H2A.Z may play critical roles in heterochromatin formation; for instance, H2A.Z is shown to be required for proper centromere function by maintaining the integrity of pericentric heterochromatin, located in the boundary region to prevent the spread of heterochromatin into euchromatin, and co-localized with heterochromatin protein HP1α at various constitutive heterochromatic domains in different mammalian cell types.29-31 In addition, depletion of H2A.Z results in the disruption of constitutive heterochromatin and defects in chromosome segregation process.32 However, H2A.Z has also been
revealed to be involved in gene activation; H2A.Z antagonizes DNA methylation along the whole genome in plants and animals and is enriched at the promoters of inducible genes to poise genes for rapid transcriptional activation.5,33-36 Genome-wide localization of H2A.Z shows that the variant flanks the nucleosome-free region at transcription start sites (TSSs) in a wide range of cell types.37-39 In addition, the variant H2A.Z is also known as an interacting partner of H3.3; H2A.Z has been revealed to be co-localized with H3.3 at active promoters and many other regulatory regions.40,41 It is of particular interest to investigate how the two variants correlate with each other in the process of gene regulation. We have investigated the coregulation of H3.3 and H2A.Z at the enhancer and promoter regions during transcription activation of RA-induced genes.23 We found that H2A.Z is actively recruited to promoters prior to gene induction and rapidly replaced during transcriptional activation. The deposition of H2A.Z into the promoter region prior to gene activation is dependent on the existence of H3.3 at the enhancer region. H3.3 knockdown greatly impairs the recruitment of the histone acetyltransferase complex and chromatin remodelers (such as Tip 60, SRCAP, and BRG1) to deposit H2A.Z at the promoter region. On the other hand, knockdown of H2A.Z does not affect the H3.3 incorporation at enhancers and promoters. It is of great interest to address how the deposition of H3.3 at enhancer region affects the incidences occurred at the promoter region, which is at least several kilobases far from the enhancer region. Notably, the two histone variants H2A.Z and H3.3 have also been found to mark CTCF (CCCTC-binding factor)-binding sites along the genome and might be important for the bindings of CTCF and cohesin to mediate higher-ordered chromatin organization.40,41 Interestingly, another recent study showed that HIRA/UBN1/ASF1a, which account for H3.3 incorporation, were found to biochemically interact with both CTCF and BRG1, a subunit of SWI/SNF which has been shown to function at the exchange of H2A.Z; in addition, genome-wide analysis showed that HIRA/UBN1/ASF1a colocalize with SWI/SNF.26 All the studies give us a clue that the histone variants may provide specialized chromatin signatures to mediate the formation of “chromatin loops” to connect the enhancers and promoters (Fig. 2).
As mentioned above, H2A.Z has been found to function both in gene activation and silencing. Many biophysical analyses have shown that H2A.Z itself can enhance the stability of histone octamers and nucleosomes reconstituted in vitro.25,29,33 Moreover, the incorporation of H2A.Z can promote the folding of chromatin arrays, including H3- and H4-terminated nucleosomes to form a compact higher-ordered structure.25,30 it is reasonable to speculate that H2A.Z would repress or poise the gene transcription. Indeed, our FRET, magnetic tweezers, AUC, and EM studies showed the stabilization and condensation effect of H2A.Z on nucleosome and/or chromatin structures.25 In addition, our in vitro transcription assay demonstrated that the incorporation of H2A.Z can inhibit transcriptional activity in the chromatin level.23 Knockdown of H2A.Z in cells impaired the compact structure of chromatin at promoter regions and promoted the RA-induced expression of Cyp26A1 and HoxA1.49 All the data agree well with the repressive role of H2A.Z in gene functions. Then, how can H2A.Z function in transcriptional activation? The apparently contradictory and complicated roles of H2A.Z might be caused by different combinations with other histone variants or specific histone modifications. H2A.Z has been found to colocalize with H3.3 in the nucleosomes located at TSS of active promoters in gene functions.49,56,57 Our biophysical analyses have shown that although the incorporation of double variant H2A.Z-H3.3 resulted in a more stable structure and nucleosome compared with the canonical H2A.Z-H3.3, it resulted in a more unstable hybrid H2A.Z-H2A nucleosomes.49 In addition, the different combinations of H2A.Z with specific histone modifications may also contribute to the complicated functions of H2A.Z in gene regulation. H2A.Z-containing nucleosomes in mammalian cells have also been found to be enriched for H3K4 methylation with less H3K9 methylation compared with the H2A-containing nucleosomes; acetylation of H2A.Z N-terminus is a hallmark of active genes while ubiquitylation and sumoylation at H2A.Z C-terminus have been implicated in heterochromatin formation and DNA repair, including the inactive X chromosome of female cells.49

H3.3 in Epigenetic Inheritance

Most recently, epigenetic regulations, including histone variants, have emerged as key players to control the cell fate by modulating the chromatin state and gene transcription during development and differentiation. Cell differentiation is believed to be mediated by lineage-determining transcription factors, which activate differentiation-specific genes by binding to the corresponding regulatory regions with appropriate chromatin features. Once a differentiated cell identity is established, the cell lineage remains stable and unlikely to change over many cell divisions. It is generally believed that the faithful inheritance of the epigenetic signature from mother to daughter cells, named as “epigenetic memory,” is crucial for the maintenance of a cell identity. It’s very interesting to investigate how a lineage-committed by undifferentiated cell maintains the ability to specifically activate the appropriate differentiation program upon differentiation signaling and how the established epigenetic information could be propagated to the next cell generation. Intriguingly, H3.3 has been shown to play a key role in global changes in the transcriptionome linked to cellular fate and has been implicated in cell differentiation; it was found at many developmental regulatory genes that are bivalent genes marked with H3K4me3 and H3K27me3 and transcription-activating H3K4me3 in mES cells.41,42 HIRA-dependent deposition of H3.3 has been shown to be required for transcriptional reprogramming of mammalian nuclei transplanted to Xenopus oocytes,43 which also has been found to facilitate the recruitment of PRC2 for proper establishment of H3K27me3 at the promoters of developmentally regulated genes in mES cells.44 For skeletal muscle differentiation, MyoD, the myogenic transcription factor, recruits Chd2, a member of the SNF2 family of chromatin remodeling enzymes, specifically at myogenic gene promoters to mediate H3.3 deposition into the regulatory regions prior to the onset of myogenic gene expression.45 Other than the faithful replication of DNA methylation by Dnmt1, which provides a plausible mechanism for the propagation of a silent gene state, the deposition of H3.3 has been found to be associated with the persistence of epigenetic memory of an active gene state in Xenopus nuclear transplant embryos.51 In addition, our results show that H3.3 is actively incorporated at enhancers prior to gene activation and primes the transcription of RA-regulated genes, indicating that H3.3 might play an important role in “epigenetic memory” for the inducible genes including RA-regulated genes. However, the mechanism by which H3.3 is inherited at enhancer regions of RA-regulated genes still remains to be clear. The replication-independent assembly of H3.3 will dilute H3.3 nucleosomes by a factor of 2 during each cell cycle. Although the canonical H3-F4 tetramers rarely split into H3-H4 dimers during cell division, approximately 10% of H3.3-H4 tetramers do experience splitting events in each cell cycle, which are remarkably enriched at cell-type
specific enhancers at genome-wide level, which may provide a possible mechanism for H3.3 inheritance at these regions.

**Conclusion**

Numerous studies have emphasized that various epigenetic mechanisms (such as DNA methylation, histone modifications, histone variants, and architectural proteins) are involved in the generation of stable and inheritable epigenetic complexity through organizing genome into functionally distinct higher-ordered chromatin domains. However, the mechanisms by which the featured chromatin signatures generated by distinct epigenetic factors are inherited from generation to generation during cell division or organism propagation in which new chromatin features need to be established, still remains unclear. In particular, whether H3.3 incorporation at enhancers is crucial for transcriptional memory or epigenetic inheritance during cell division or organism propagation will need further investigation. In this context it is of great interest to analyze whether H3.3 can cooperate with other histone variants (such as H2A.Z) or DNA and/or histone modifications to generate a transcriptionally permissive state for the differentiation-specific genes by modulating the chromatin dynamics at regulatory regions of the genome during development and differentiation. In future studies in order to illuminate the roles of histone variants in the regulation of the higher-ordered chromatin organization, it will also be of great interest to analyze the dynamics of histone variants upon gene activation during development by

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**ChiP-seq assays and CRISPR/Cas or TALEs imaging techniques developed recently.**

**Disclosure of Potential Conflicts of Interest**

No potential conflict of interest was disclosed.

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