Chapter 1

Overview on structure and function of chromatin

by Tatsuo Nakayama and Masami Nakayama

SUMMARY

The fundamental repeating unit of chromatin, nucleosome, consists of a histone octamer (comprising two molecules of each of core histones H2A, H2B, H3 and H4), ~146 base pairs of DNA wrapped around it, a variable length (0-80 base pairs) of linker DNA and linker histone H1 (or H5) (in higher eukaryotes). Alterations in chromatin structure are preferentially involved in almost all of DNA-utilizing processes, including gene expression. Of various epigenetic mechanisms of chromatin, acetylation and deacetylation of core histones are the most common/important modifications. The acetylation levels of core histones are cooperatively/precisely controlled by histone acetyltransferase(s) and deacetylase(s), each member of which plays particular roles in expressions of cell functions.

In eukaryotes genomic information is preserved in a complex structure, chromatin, which participates in packaging genomic DNA into nucleus efficiently and providing the place for various DNA-utilizing reactions, such as replication, recombination, repair, gene expression and so on. The organization and packaging of chromatin are achieved through the addition of numerous kinds of proteins, including histones, to the DNA molecule. A typical model for the hierarchy of chromatin structure is as follows [1-8]. The basic structural unit of chromatin, nucleosome, consists of a histone octamer, comprising two molecules of each of core histones H2A, H2B, H3 and H4, and approximately 146 base pairs of DNA wrapped around it. With a variable length (0-80 base pairs) of linker DNA and linker histone H1 (or H5) (in case of higher eukaryotes), nucleosome constitutes the fundamental repeating unit of chromatin. Upon the assistance of a number of non-histone proteins, including high-mobility group (HMG) proteins, the nucleosome arrays are assembled into a higher order chromatin structure. Genomic DNA folds around nucleosomes to form 10 nm fibers, which fold helically into 30 nm chromatin fibers. These 30 nm fibers further form loops observed in the prophase chromosome axis that coils to form the fully condensed metaphase chromosome.

Because histones (H2A, H2B, H3, H4, H1, and/or H5) are essential for the maintenance of chromatin structure, numerous numbers of each histone subtype must be rapidly/surely accumulated in nucleus and quickly/correctly incorporated into nucleosome prior to cell division. To supply a large amount of every histone subtype, following three distinct manners exist in eukaryotes. 1) The histone genes should be present in multiple copies in most of higher eukaryotes, ranging from several dozen to hundreds, although yeast has two genes for each of core histones [4, 9]. 2) The levels of the histone mRNAs should be mainly controlled at post-transcriptional step [10]. 3) There is an attractive compensatory regulation mechanism, by which the mRNA levels of histone subtypes are precisely kept in a stoichiometric balance [11-15].

On the other hand, alterations in chromatin structure are preferentially involved in the

above-mentioned DNA-utilizing processes. Concerning gene expression, besides the DNA methylation [16], there are at least three remarkable manners through chromatin structure changes as follows: 1) regulation by variants of each histone subtype, 2) chromatin remodeling and 3) post-translational modification.

First, several different variants with amino acid substitution(s) have been reported for most histone subtypes [9, 17, 18]. The nature of histone variants as to the regulation of gene expression has reported in Saccharomyces cerevisiae, Drosophila melanogaster, Xenopus, Tetrahymena thermophila and so on [19-24]. In addition, six H1, three H2A, four H2B and two H3 variants exist in chickens, in which the nucleotide sequences of almost all histone genes were determined [9], and these variants were reported to regulate gene expression [14, 15, 25-27]. These findings revealed that besides the vital role in the chromatin organization, histone variants participate in regulation of gene expression.

Secondly, chromatin structure should function as a transcriptional repressor in vivo because it usually inhibits the binding of transcription factor proteins to their binding sites. At the first step of gene activation, alterations in chromatin (nucleosome) structure, chromatin remodeling, surrounding promoter and/or enhancer regions of DNA, should allow the binding of transcription factors. A particular enzymatic activity has been reported to be necessary in this chromatin remodeling process. Many different chromatin-remodeling complexes, such as NURF, CHRAC, ACF, SWI/SFF, ISW1, ISW2, RSF, WCRF and others, have been identified independently by distinct assays in various organisms, i.e., Drosophila melanogaster, yeast and mammals and so on [28-30]. All of these complexes are functionally/biochemically different each other but ubiquitously possess ATPase activity, which disrupts the interaction between DNA and histones [31]. Detailed reviews on the chromatin remodeling have been done elsewhere [32-34].

Thirdly, histone modification is one of the most common and important epigenetic mechanisms [35-40]. Post-translational modifications of histones, such as acetylation, phosphorylation, methylation, ubiquitination and sumoylation, mainly occur at their N- and C-terminal tails. Reviews concerning the latter four have been done elsewhere in detail [41-46]. Because a large number of topics concerning the former one have also been reviewed [35-40, 47-74], based on those review articles, here, we briefly discuss the functional impact of alterations in chromatin structure based on the acetylation of core histones. The molecules of core histones have been divided into three functional domains: histone-fold regions, diverse extensions and histone tails that extend outside the nucleosome core particle. Surprisingly, approximately 50 years ago the chemical modifications of core histones with the acetyl group were first proposed to be of fundamental importance as to activation of gene expression in eukaryotes [75]. In fact, it has been established not only that acetylated core histones are preferentially associated with transcriptional active chromatin, but also that the acetylation occurs at conserved Lys residues in the N-terminal tails of core histones. In addition, the positions of particular Lys residues

modified with the acetyl group have remained nearly invariant throughout eukaryotic evolution. Remarkably, the huge knowledge about the importance of the acetylation of core histones in regulation of gene expression through chromatin conformation changes has been rapidly accumulated not only in the basic science as mentioned above [35-40, 47-74] but also in the clinical medicine [76-79] year by year. The acetylation of the particular Lys residues should induce an open chromatin conformation that allows the transcription machinery access to promoters. The acetylation level is precisely/cooperatively controlled with chromatin-modifying enzymes, histone acetyltransferase(s) (HATs) and deacetylase(s) (HDACs). HATs transfer the acetyl group to the Lys residues at the N-terminal tails of core histones to promote euchromatin formation. In contrast, HDACs remove the acetyl group from acetylated Lys residues of core histones for gene silencing. Thus, the histone acetylation controlled by HATs and HDACs plays critical roles in the modulation of chromatin topology and the regulation of gene expression in eukaryotes. As mentioned above, a number of HAT and HDAC family members have been identified in several organisms and their specific functions have been reviewed in detail. For instance, we have clarified individual roles of particular members of HATs and HDACs in the chicken DT40 cells by gene targeting techniques as follows. GCN5 is involved in gene expressions of various important factors and enzymes and also the IgM H-chain [80-87], and HAT1 contributes to recovery of DNA damages and integrity of histone H3-H4 containing complex [88, 89]. In addition, HDAC2 indirectly/mainly regulates gene expressions of IgM H- and L-chains through transcription regulations of Pax5, EBF1, OBF1, Aiolos, E2A and other genes [90-92], and HDAC3 is essential for viability and important for apoptosis progression [93, 94].

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