Chapter 1

Overview on structure and function of chromatin

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SUMMARY

The fundamental repeating unit of the chromatin, the nucleosome, consists of a histone octamer (comprising two molecules of each of core histones H2A, H2B, H3 and H4), approximately 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 the chromatin structure are preferentially involved in almost all of DNA-utilizing processes, including gene expression, DNA replication, recombination, repair and others. Of various epigenetic modifications of the chromatin, acetylation and deacetylation of core histones are the most common and important modifications. Acetylation levels of specific Lys residues of core histones are cooperatively and precisely controlled by chromatin-modifying enzymes, such as histone acetyltransferases (HATs) and histone deacetylases (HDACs), each member of which plays specific roles in expressions of normal cell functions.

In eukaryotes genome information is preserved in a complex structure, the chromatin, which efficiently participates in packaging genomic DNA into nucleus and also provides the place for various DNA-utilizing reactions, such as replication, recombination, repair, gene expression and others. The organization and packaging of the chromatin are achieved through the addition of numerous kinds of proteins, including histones and various non-histone proteins, to the DNA molecule. A typical model for the hierarchy of the chromatin structure is as follows [1-8]. The basic structural unit of the chromatin, the 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), the nucleosome constitutes the fundamental repeating unit of the 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 the 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, and H1 or H5) are essential for the maintenance of the chromatin structure, numerous numbers of each histone subtype must be rapidly and surely accumulated in nucleus, and quickly and correctly incorporated into the nucleosomes prior to cell division. To supply a large amount of every histone subtype, following three distinct ways exist in eukaryotes. 1) The histone genes are present in multiple copies in most of higher eukaryotes, ranging from several dozens to hundreds, although yeast has two genes for each of core histones [4, 9]. 2) The mRNA levels of every histone subtype are mainly controlled at a post-transcriptional step [10]. 3) There is an attractive compensatory regulation mechanism, by which the mRNA levels of each of histone subtypes are

precisely kept in a stoichiometric balance [11-15].

Moreover, as mentioned above, alterations in the chromatin structure are preferentially involved in the varied kinds of DNA-utilizing processes. Concerning gene expressions, besides the DNA methylation [16], there are at least three remarkable ways by means of the chromatin conformation (structure) changes as follows: 1) the regulation by variants of every histone subtype, 2) the chromatin remodeling and 3) the post-translational modification.

First, several different variants with amino acid substitution(s) have been reported for most of histone subtypes [9, 17, 18]. The nature of these histone variants as to the regulation of gene expressions has reported in Saccharomyces cerevisiae, Drosophila melanogaster, Xenopus, Tetrahymena thermophile, etc. [19-24]. We determined the nucleotide sequences of almost all histone genes of chickens and reported that six H1, three H2A, four H2B and two H3 variants exist at least [9]. In addition, we reported that most of these variants separately regulate gene expressions in chicken DT40 cells by gene targeting techniques [14, 15, 25-27]. These findings revealed that besides the vital role in the chromatin organization, histone variants surely participate in regulation of gene expressions.

Secondly, the chromatin structure acts as a powerful 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 the chromatin (nucleosome) structure, the chromatin remodeling, surrounding transcriptional elements of DNA (such as promoter, operator, enhancer, etc.) allow the binding of transcription factors. Several specific enzymatic activities have 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 independently identified by distinct assays in various organisms, i.e., yeast, Drosophila melanogaster, mammals, etc. [28-30]. All of these complexes are functionally and biochemically different with 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, the chemical modification of histones is one of the most common and important epigenetic modifications [35-40]. Post-translational modifications of histones (such as acetylation, phosphorylation, methylation, ubiquitination, sumoylation, ADP ribosylation, etc.) mainly occur at their N- and C-terminal tails. Reviews concerning the last five have been done elsewhere in detail [41-46]. Because a large number of topics concerning the first one have also been reviewed in numerous articles [35-40, 47-74], here, we briefly discussed the functional impact of alterations in the chromatin structure depending on the acetylation and deacetylation levels 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 expressions in eukaryotes [75]. In fact, it has been established that the acetylation and deacetylation occur at the conserved and specific Lys residues in the N-terminal tails of core histones, and then the acetylated core histones are preferentially associated with the transcriptional active chromatin. In addition, the positions of the conserved Lys residues modified with the acetyl group have remained nearly invariant throughout eukaryotic evolution. Remarkably, the huge knowledge about the importance of the acetylation and deacetylation of core histones in the regulation of gene expressions by means of the chromatin conformation changes have 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 conserved Lys residues induces an open chromatin conformation that allows the transcription machinery access to promoters. The acetylation and deacetylation levels are precisely and cooperatively controlled with chromatin-modifying enzymes, such as histone acetyltransferase(s) (HATs) and histone deacetylase(s) (HDACs). Members of HATs transfer the acetyl group to the conserved Lys residues at the N-terminal tails of core histones to promote the euchromatin formation. In contrast, members of HDACs remove the acetyl group from the acetylated Lys residues of core histones for gene silencing. Thus, the histone acetylation and deacetylation levels controlled by HATs and HDACs play critical roles in the modulation of the chromatin topology and in the regulation of gene expressions in eukaryotes. As mentioned above, a number of HAT and HDAC family members have been identified in several organisms and their detailed and specific functions have been reviewed by many research groups. We also clarified individual roles of specific members of HATs and HDACs in 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 both the recovery of DNA damages and the integrity of histone H3-H4 containing complex [88, 89]. In addition, HDAC2 indirectly and mainly regulates gene expressions of IgM H- and L-chains through opposite regulations of gene expressions of Pax5, EBF1, OBF1, Aiolos, E2A and others [90-92], and HDAC3 is essential for viability and important for apoptosis progression [93, 94].

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