



ULTRA STRUCTURE OF CHROMATIN ORGANIZATION

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Abstract

In eukaryotes, genomic DNA is packaged in chromatin in the cell nucleus. DNA accessibility depends on chromatin structure and dynamics, which essentially control DNA-related processes, including transcription, DNA replication, and repair. Nucleosomes, the repeating building blocks of chromatin, vary in the composition of their histone protein components. All factors affectin nucleosome structure and dynamics, nucleosome-nucleosome interaction interfaces, and binding of linker histones or other chromatin-binding proteins must be considered to understand the organization and function of chromatin fibers. In this review, we provide a summary of recent advances in the structure of chromatin fibers in vitro and in the nucleus, highlight studies on the dynamic regulation of chromatin fibers, and discuss their related biological functions and abnormal organization in disease.

Key words- Chromatin fiber, Linker histone, Structural dynamics, DNA Replication, Transcription

Introduction

Each human cell contains about 2 meters of DNA if we stretch it from end to end. The nucleus of a human cell is only about 6 μm in diameter, but it contains all of the DNA. DNA needs to be packed tightly to fit into the cell nucleus, it accomplishes this by wrapping itself around the histone protein to form a nucleosome. [1]. Repeating units of the nucleosome structurally and functionally make up the chromatin unit. So, chromatin is a mixture of proteins and DNA that condense to form chromosomes. In vivo, eukaryotic genomes are organized into chromatin, a DNA-protein complex whose basic repeating unit is the nucleosome [2]. The nucleosome consists of 147 base pairs of DNA wrapped 1.7 times around an octamer of histone proteins (two each of histones H2A, H2B, H3, and H4). Polynucleosomal pathways appear by electron microscopy as beads on a string, with nucleosomes seen as beads and the intervening linker DNA being the string [3].

First, the location of a nucleosome relative to the underlying genomic sequence affects the accessibility of regulatory sequences, so precise translational positioning of nucleosomes can be of great regulatory consequence. In addition, there are several isoforms of histones that combine to form a number of different octamers. Finally, histones undergo a bewildering array of covalent modifications. Since the basic composition of nucleosomes was described in 1974, chromatin structure has been of increasing interest as it is involved in processes ranging from recombination to transcription to cell cycle control and cancer.

For three decades, most of our knowledge of chromatin structure came from intensive single-gene approaches at loci such as the chicken globin locus or the yeast PHO5, GAL1-10, and HIS3 promoters. With the advent of the genomics era, brought on by the availability of whole genome sequences and technologies such as microarrays and high-throughput sequencing, we can now measure many aspects of chromatin structure across whole genomes in a single experiment. We start with a brief overview of genomics technologies used to study chromatin structure.

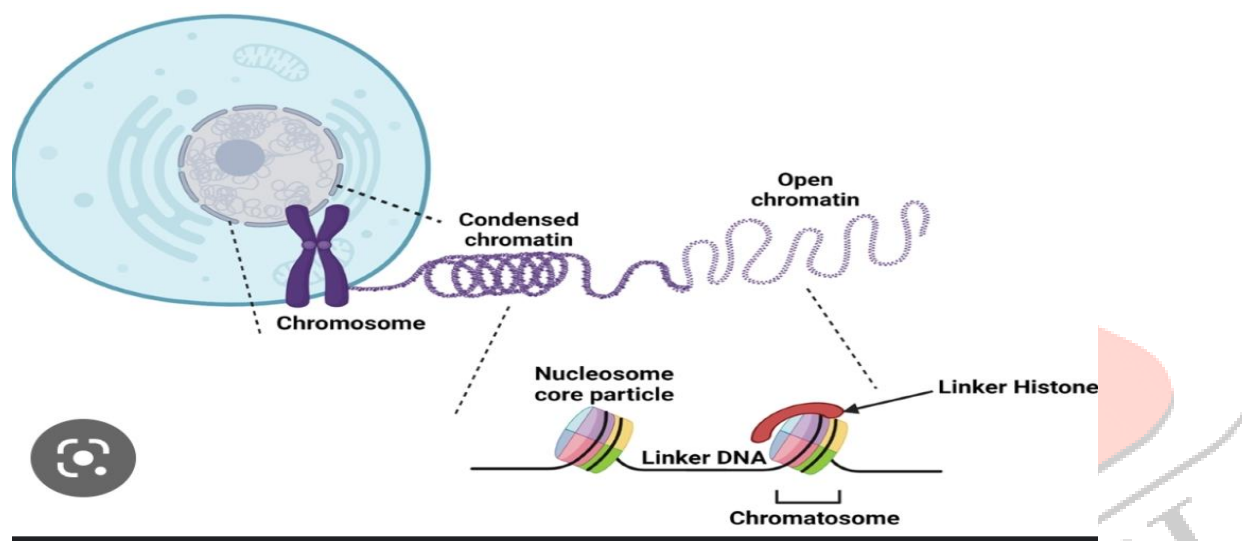
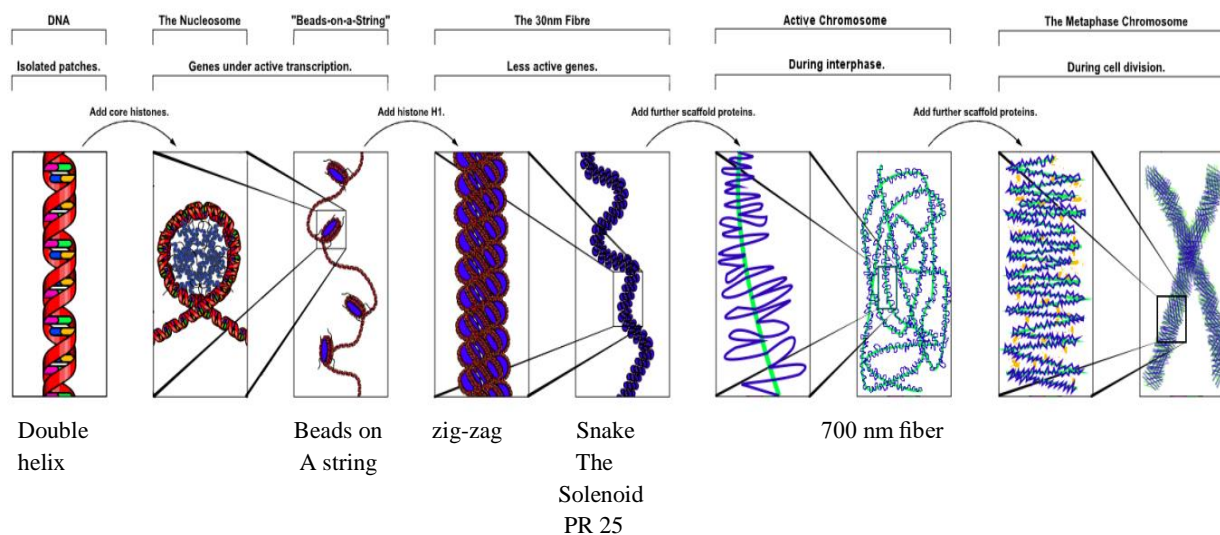


Fig. 1 Overview of the different levels of DNA compaction.

The first higher-order structure of the chromatin is the nucleosome, which is composed of 145–147 bp of DNA wrapped around a H3/H4 tetramer and two H2A/H2B dimers. The histone H1 linker binds DNA fragments that link two nucleosomes to form the chromatosome. The addition of H1 promotes internucleosomal interactions and the formation of the 30 nm chromatin fiber. The highest level of DNA compaction is the metaphasic chromosome, observable during cell division.

Chromatin structure

In Chromatin Structure human genetic information, carried by DNA, consists of 3×10^9 base pairs (bp), i.e., 6×10^9 bp in the nucleus of a diploid cell [4]. This corresponds to approximately 2 m of DNA contained in a core of 5 to 10 μ m in diameter [5]. DNA is condensed by association with small basic proteins called histones, allowing for 10,000- to 20,000-fold compression (Figure 1) [6].



Yeast chromatin overview

In general, the lessons learned from studies of chromatin in the model yeast *Saccharomyces cerevisiae* also apply to multicellular organisms (there are of course). We therefore first discuss genomic studies of chromatin structure in yeast and then turn to additional features found in mammals.

An overarching paradigm emerging from genomic studies of chromatin is that common patterns (which can be conceptualized as motifs) are emerging that are widespread but not ubiquitous. These stereotyped structures often provide a deep insight into the general rules underlying the establishment of chromatin architecture. However, not all promoters (for example) in yeast look like the typical pattern, and the deviations from the average behavior often reveal important regulatory mechanisms at play. Therefore, in each section, we first emphasize common patterns and then point out examples of genomic loci that deviate from the typical pattern.

Nucleosome location

Nucleosome occupancy has been studied in yeast using low resolution DNA microarrays [7, 8], high resolution tiling oligonucleotide microarrays [9-11], and most recently ~4 bp resolution high-throughput sequencing (12-14). In general, any higher resolution study confirms previous results, while higher resolution additionally allows for the appreciation of new features. A notable surprise in genomic maps of nucleosome locations has been the extent to which nucleosomes are well positioned in the population.

Yeast open reading frames are generally characterized by a severely nucleosome-depleted region (often called the nucleosome-free region or NFR, but see below) found upstream and surrounded by two well-positioned nucleosomes.

Histone dynamics

Histones, like other proteins, are synthesized in the cytoplasm. To prevent histone mismatch, so-called histone chaperone proteins bind to newly synthesized histones, which are involved in transporting histones to the nucleus [7]. These chaperones also prevent non-specific DNA binding and histone degradation. ATP-dependent chromatin remodeling complexes are associated with these histone chaperones and are required for nucleosome positioning. These complexes are involved in the incorporation of histone variants and affect nucleosome spacing, gliding, or removal.

Histones from the core particle of the nucleosome include a secondary structure known as a histone fold, amino- and carboxy-terminal extensions, an amino-terminal tail, and a carboxy-terminal tail for H2A. The histone fold consists of three helices connected by loops according to a 1-L1-2-L2-3 model. The 1- and 3-helix are relatively short (9 to 14 amino acids), in contrast to the 2-helix with an average of 29 amino acids [8,9]. The secondary structure of the histone fold is retained despite low sequence retention between the four core particle histones of the nucleosome. Histone folding promotes protein-protein interactions that are used to heterodimerize H2A/H2B and H3/H4 [10].

N-terminal ends do not have a defined secondary structure. The linker histone is composed of unstructured amino- and carboxyterminal tails and an apolar central globular area. The C-terminal tail is basic [11].

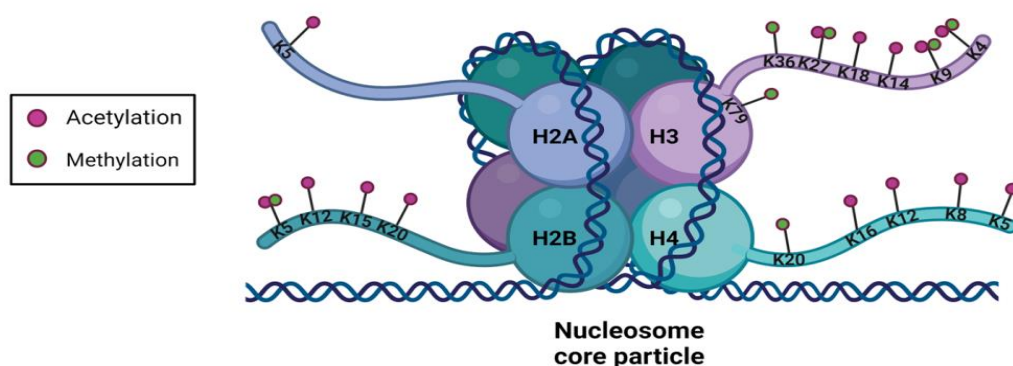


Figure 2. Structure of a nucleosome and main sites of methylation and acetylation in histones. Posttranslational modifications of the histones are mostly performed on the amino-terminal tails of the histones accessible to the epigenetic writer and eraser. Acetylated residues are in pink and methylated ones are in green.

Conserved Features of Chromatin Structure

Many features of chromatin structure are conserved from yeast to mammals. Nucleosome placement appears to be constrained by some of the same sequence preferences as in yeast, since patterns of dinucleotide repeats identified in yeast nucleosomes and sequences depleted in yeast nucleosomes partially alter nucleosome occupancy in chicken and can predict human chromatin [12, 13].

Nucleosome-exclusive sequences are common but not ubiquitous attributional start sites (TSSs) of mammalian genes and are enriched in ubiquitously expressed genes [14]. Mammalian chromatin also has nucleosome-free regions (NFRs) of approximately 200 bps centered 85 bp upstream of the transcription start site and surrounded by positioned nucleosomes; this has been documented indirectly by genome-wide measurement of DNase hypersensitive sites (DHSs) (15) and by direct measurements of histone occupancy (88-90). Flanking NFRs with well-positioned nucleosomes is consistent with the notion that NFRs themselves, or the machinery that forms them, play an instructive role in nucleosome positioning.

Diversification of rules for nucleosome occupancy

We have summarized the chromatin state of a typical transcriptionally active mammalian gene. Despite the many overlapping features between yeast and metazoan chromatin structure, differences can also be identified. Mammalian genes are associated with an NFR when actively transcribed [16] or when a preinitiation complex has been assembled [17], but not for untranscribed genes, and constitutive sequence-programmed NFRs

appear to be uncommon. In mammals and flies, Pol2 and H3K4me3 can be detected at many genes without appreciable mRNA production, suggesting the widespread existence of paused RNA polymerase complexes ready for transcription at the beginning of many genes (97-99), in contrast to yeast (but see reference 100). The mammalian nucleosome +1 is located at +40 bp relative to the TSS for transcribed genes [16] but at +10 for polymerase-arrested genes.

Clinical Relevance

A deviation in DNA organisation has broad therapeutic implications. Many histone methylation disorders, such as the alpha thalassemia X-linked intellectual impairment syndrome, Rubinstein-Taybi syndrome, Coffin-Lowry syndrome, and Rett syndrome, serve to emphasise this [18] [19][20][21][22][23]. The fundamental idea behind the study of epigenetics is that DNA packing around histones directly influences how genes are expressed. The contribution of variable gene expression to a range of pathologic processes involved in cancers, neurological disorders, and even consciousness, among many other disease states, is suggested by the current body of evidence. However, the extent to which variable gene expression contributes to clinical presentations is still being actively determined [24] [25][26]

Conclusion

Genome mapping studies provide unprecedented insight into the structure of chromatin in eukaryotes. In general, mapping histone tags provides insight into the mechanism of deposition of the tag, not necessarily the function of the tag. In yeast, sequence rules and RNA polymerase together account for much of the chromatin structure observed in midlog cultures. Many aspects of chromatin structure are conserved from yeast to humans, but human cells exhibit diversification of almost all classes of chromatin regulatory machinery.

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