Nucleosomes: Structure and Function

Introductory article

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The structure of the nucleosome core particle, the basic repeating unit in eukaryotic chromatin, allows us to view the role of histones in regulating transcription, and in assembling specialized chromatin domains in a structural context. The organization of eukaryotic DNA into chromatin has fundamental implications for our understanding of all cellular processes that use DNA as a substrate.

Introduction

The genetic information of a single eukaryotic cell is stored in DNA molecules that are in total over 2 m long, but compact in the cell's nucleus to nearly one millionth of this length. This is achieved by a hierarchical scheme of folding and compaction into protein–DNA assemblies called chromatin. At the first level of organization, two tight superhelical turns of DNA (147 base pairs in length) are wrapped around a disc-shaped protein assembly of eight histone molecules to form the nucleosome core particle. Extension of the DNA to 170–240 base pair length, and the addition of linker histone H1 gives rise to the nucleosome which forms the basic repeating unit in chromatin. Hundreds of thousands of nucleosomes are further organized in multiple higher levels. Because of its packaging in nucleosomes, the structure and accessibility of DNA that predominates in the living cell deviates dramatically from that of linear, 'naked' DNA, as seen for the first time in the high-resolution X-ray structure of the nucleosome core particle. This has fundamental implications for our understanding of all processes that use DNA as a substrate, such as transcription, replication, DNA repair and recombination. Chromatin can both promote and impede these processes depending on structural context, and thus plays a central role in their regulation. Eukaryotic cells have developed elaborate mechanisms to modulate inherently dynamic chromatin structures in a regulated manner.

Structure of the Nucleosome Core Particle

The nucleosome core particle consists of an octameric protein core around which 147 base pairs of DNA are wrapped in 1.65 turns of a left-handed superhelix (**Figure 1a,b**). The protein core itself is composed of two copies each of the four core histone proteins H2A, H2B, H3 and H4. The core histones share a structurally conserved motif, the histone fold, averaging about 70 amino acids (**Figure 2a**). Histone fold extensions are structured regions outside the histone fold that are responsible for protein–protein interactions within the histone octamer, for defining the surface of the nucleosome core particle, and also contribute to DNA binding. These extensions are structurally not conserved between the four core histones, and are variable in length. The flexible histone tails are defined as those parts of the histone proteins that extend from the confines of the DNA superhelix. They do not form an integral part of the histone octamer, but may contribute minimally to DNA binding in the context of a mono-nucleosome.

Like every other structure that has been determined at high resolution, the structure of the nucleosome core particle may be accessed and displayed in the *Protein Data Bank* (entry code 1AOI). The complex was featured as 'molecule of the month of July' by the protein data bank (see http://www.rcsb.org/pdb/molecules/pdb7_1.html for further discussion).

The histone fold

The histone fold consists of three α helices connected by short loops. Two short, 10–14 residue helices flank a longer, 28 amino acid central α helix, creating a shallow slot. In solution, the histone fold always forms a tight homo- or heterodimer with another histone fold protein, stabilized through a large interaction interface by the antiparallel arrangement of the two long α2 helices (**Figure 2b**). Dimerization leads to the alignment of the L1 loop of one histone with the L2 loop of the other at the edges of the crescent-shaped dimer and a close juxtaposition of the N-termini of the two α1 helices at its apex. This arrangement forms three DNA interaction modules per histone fold dimer, two L1L2 sites, and one α1α1 binding site (**Figure 2b**). Despite the low degree of sequence homology between the amino acid sequences of the four core histone proteins, their histone fold motifs can be superimposed with little divergence.

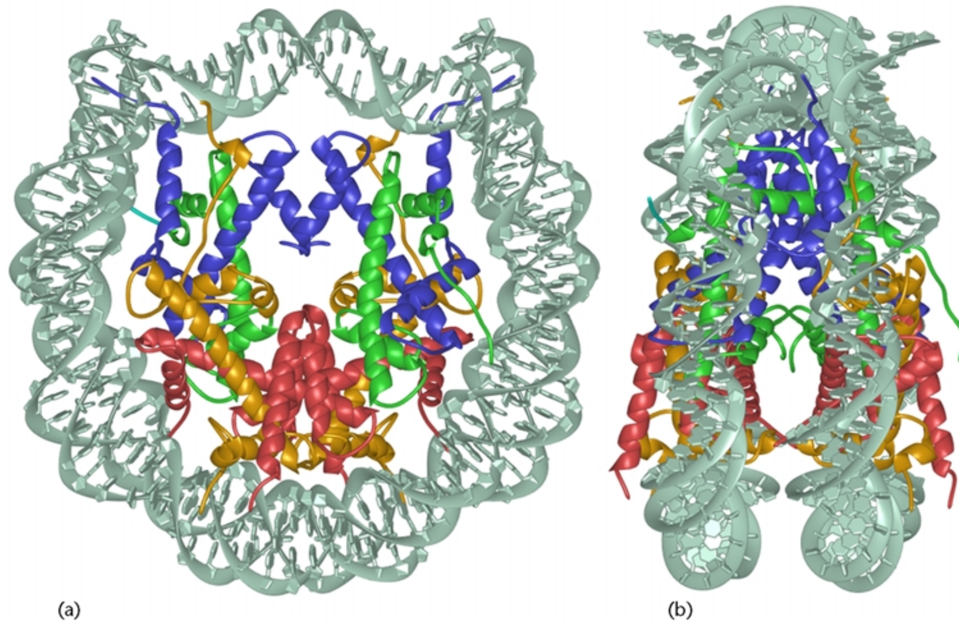

Figure 1 Overview of the nucleosome core particle structure, viewed in two different orientations. This schematic representation is derived from the high-resolution crystal structure, and demonstrates how a 5-fold compaction of DNA is achieved by wrapping it around the histone octamer core. α Helices of the histone proteins are shown as spirals. H3 is coloured blue, H4 green, H2A yellow and H2B red. The DNA is shown in grey. (a) The nucleosome core particle viewed down the superhelical axis. (b) The same structure is rotated by 90° around the *y*-axis to emphasize the disc-like shape of the particle.

The histone fold in other proteins

Archaebacteria, but not eubacteria, have a very minimal set of histone-like proteins. Tetramers of two histone-like proteins (that do not contain extensions or tails) are responsible for the protection and compaction of the very small archaebacterial genome.

Surprisingly, the histone fold has also been identified in a number of other proteins, most of which are involved with transcription regulation. Some subunits in TFIID (a large multi-subunit assembly that is required for the proper start of RNA polymerase II) and subunits of large histone modification complexes also contain this fold. It is tempting to hypothesize that the histone fold motif in these factors may aid the formation of nucleosome-like structures on DNA. However, this does not appear to be a general rule, since many of the proteins mentioned above fail to bind to DNA on their own. An excellent source of histone sequence alignments and a compilation of non-histone proteins with this fold can be found in the *Histone Sequence Database*.

The histone octamer

The histone octamer is best viewed as an arrangement of histone fold dimers. Two histone fold pairs composed either of H2A and H2B, or H3 and H4, form heterodimers that each organize 30 base pairs of DNA, using the L1L2 and α1α1 binding sites as DNA-binding motifs (**Figure 2b**). Two H3–H4 dimers are arranged in a tetramer via a four-helix bundle structure composed of helices from two H3 molecules. This tetramer organizes the central 60 base pairs of nucleosomal DNA.

A very similar, but heterologous four-helix bundle structure formed by residues of H4 and H2B tethers one (H2A–H2B) dimer to one half of the histone $(H3–H4)_2$ tetramer (**Figure 2c**). This interaction is not stable in the absence of DNA, and is aided by a histone fold extension of H2A (the docking domain) that interacts with the other half of the histone $(H3–H4)_2$ tetramer. The H2A docking domain also positions an H3 histone fold extension (H3αN) to interact with the 10 penultimate base pairs of nucleosomal DNA.

The histone octamer is not stable in solution under physiological conditions. Whereas the four-helix bundle structure that holds the $(H3-H4)_2$ tetramer together persists in the absence of DNA, the dimer–tetramer interaction is not observed. Consequently, (H2A–H2B) dimers and $(H3–H4)_2$ tetramers are the physiological subunits in the absence of DNA. This has important implications for the *in vivo* and *in vitro* assembly of nucleosomes (see below).

Histone tails

The flexible tails of the core histones are the sites of reversible modification whose central role in many cellular

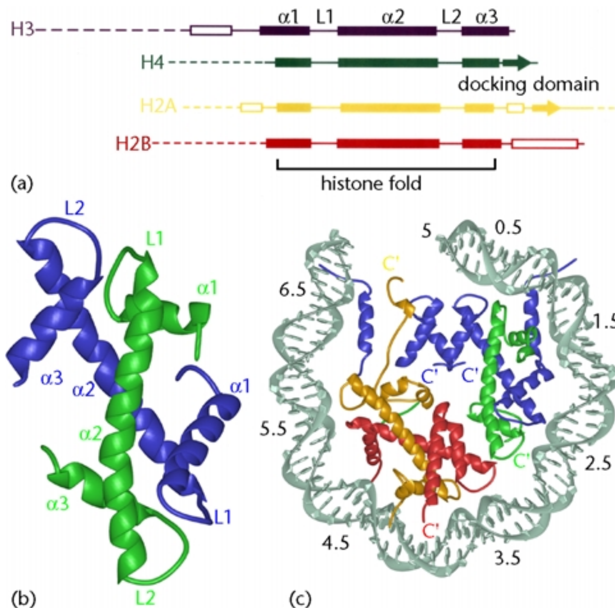

Figure 2 Architecture of the histone fold and of the nucleosome core particle. (a) Schematic overview of the four histone proteins H3, H4, H2A and H2B. α Helices of the histone fold are shown as solid boxes, α helices and β strands of the histone fold extensions are shown as open boxes and arrows, respectively. Histone tails are shown as dotted lines. The length of α helices, β strands, loops and tails is shown to scale. The components of the histone fold (α1, L1, α2, L2, α3), and the location of the H2A docking domain are indicated. (b) A histone fold dimer (here shown for H3 and H4, shown in blue and green, respectively) is formed by the antiparallel arrangement of two histones. α Helices and loops of the histone fold are indicated (compare with (a)). The orientation is similar to that in (c). (c) The architecture of the histone octamer is revealed by depicting only half of the DNA and associated proteins, in the same view as in **Figure 1a**. Unlike (b), this figure shows not only the histone fold regions, but also histone fold extensions and part of the tails. The C-terminus of each histone protein is labelled C′. Note that most of the tails are disordered and are therefore not included in this picture. Regions of protein–DNA interaction are numbered from the centre of the DNA outwards.

processes will be discussed in more detail below. Histone tails vary in length between ∼40 amino acids (H3) and ∼15 amino acids (H2A); but specialized histone variants can have much longer tails. The tails are located in the N-terminal region of the protein; H2A also has a C-terminal tail of variable length (**Figure 2a**). The sequence alignment of histones from different organisms, and between different histone variants reveals that the histone tails are much less conserved than the histone folds and extensions (see http://genome.nhgri.nih.gov/histones/ for alignments).

Importantly, not all histone tails are created equal: early genetic experiments in yeast have shown that the roles of H3 and H4 tails are different from those of H2A and H2B tails. Tails may also assume different roles (and/or structures) depending on their state of modification, on local chromatin structure, and on the presence of nuclear factors.

No electron density is seen for most of the histone tail regions in the crystal structure of the nucleosome core particle. This is due to static or dynamic disorder of the tails within the crystal, and suggests that at least under these conditions, they do not interact with the DNA and do not play a significant role in stabilizing the nucleosome core particle, in accordance with biochemical studies.

Experiments using the more physiological nucleosomal arrays (see below) point to a role of the histone tails in the organization of higher order structure. Support for this comes from the crystal structure, in which the basic H4 N-terminal tail makes an essential contact with an acidic patch on the histone octamer surface of a neighbouring nucleosome core particle. Factors that specifically recognize histone tails may assist in the formation of alternative chromatin structures. Tails also may recruit chromatin remodelling factors that make nucleosomal DNA more accessible for transcription.

Posttranslational histone modification

The tails of all histone proteins are dynamically modified in a highly regulated manner during chromatin assembly, during the establishment of specific transcriptional patterns, and during mitosis and development. Modifications include acetylation, phosphorylation, ubiquitination, methylation, and ADP-ribosylation. The biological significance of these modifications is not well understood. First reports on the reversible modification of histone proteins date from the early 1960s. Although a role of these modifications in locally altering chromatin structure to facilitate transcription in a chromatin context was suggested around the same time, it took almost 25 years before the subject was picked up by a wide number of researchers. Over the past few years, the long-standing idea that covalent modification of histones can play a role in determining states of gene activity has been confirmed.

Chemically, the attachment of an acetyl group to a lysine results in the neutralization of its charge. Given the role of histone tails in the organization of higher order structure, it is tempting to speculate that acetylation leads to decondensation of repressive chromatin structures, resulting in a more accessible DNA substrate. Consequently, the removal of an acetyl group will stabilize chromatin in a more condensed form. A number of co-activators that are required for transcriptional activation from a chromatin template have been shown to be histone acetyltransferases (HATs), and conversely, many co-repressors act as deacetylases (HDACs).

Protein–DNA interaction

The massive distortion of DNA into a superhelix is brought about by the tight interaction between the rigid framework of the histone octamer and the DNA at 14

independent DNA-binding sites, numbered 0.5–6.5 in **Figure 2c**. The flat, wedge-like surface of the histone octamer displays a continuous basic groove along the surface around which the negatively charged DNA is wound. DNA binding is accomplished mostly by L1L2 loops or α1α1 DNA-binding motifs formed by histone fold dimers. The last turn of the DNA (6.5 in **Figure 2c**) is organized by a histone fold extension of H3 (H3 αN, **Figures 1b** and **2c**). Since interactions at this site are by far the weakest in the whole nucleosome core particle, this helix is most likely not interacting with DNA in the absence of the (H2A–H2B) dimer. Thus, removal of one (H2A–H2B) dimer from the nucleosome core particle releases at least 40 base pairs from the nucleosome.

The histone octamer is able to organize the cell's entire genome, irrespective of the DNA sequence context. Consequently, not a single direct contact with a base pair is observed in the structure of the nucleosome core particle. Interactions are made exclusively at the minor groove of the DNA, and are characterized by extensive hydrogen bonding between the protein's main chain amide atoms and the phosphate oxygen atoms of the DNA backbone.

Most of the histone sequence is involved directly in either protein–protein or protein–DNA interaction. This in part explains the extremely high degree of sequence conservation of core histones throughout the evolution of histones. In fact, histones are among the most highly conserved proteins known.

Chromatin assembly

The modular architecture of the histone octamer is reflected in the assembly of nucleosome core particles. *In vivo*, chromatin assembly factors first deposit an $(H3–H4)_2$ tetramer on the DNA, to which the (H2A–H2B) dimer is escorted by histone chaperons. Expression of the bulk of histone proteins and the assembly of newly replicated DNA into chromatin is tightly coupled to replication. However, chromatin assembly factors also play an important role during DNA repair.

Most *in vitro* nucleosome assembly methods make use of the fact that the $(H3–H4)_2$ tetramer binds to the DNA at significantly higher ionic strength than the dimer. Histone dimers, tetramers and DNA are mixed at high ionic strength, and the salt concentration is lowered gradually to allow binding of the $(H3–H4)_2$ tetramer to the DNA, followed by binding of the (H2A–H2B) dimer. Systems using purified assembly factors (see above), or crude cell extracts are also in use, and are preferred for the preparation of long, evenly spaced nucleosomal arrays.

The path of the DNA

Nucleosomal DNA does not follow the path of an ideal superhelix, but exhibits regions of high curvature adjacent to regions that are almost straight (**Figure 2c**). This path is determined predominantly by histone/DNA contacts and is independent of the DNA sequence. Compared to linear B-form DNA, the major and minor grooves are highly compressed and deep as they face the histone octamer, and extended (flattened) significantly when exposed at the outside. The deviations from the canonical minor groove width for straight B-form DNA are most extreme in the highly curved areas. In some areas, the DNA is distorted in a manner that disfavours proper base pairing.

The close spatial proximity of the two turns of the DNA superhelix with a pitch of 24 Å, and the periodic variation of double helix parameters with a mean of 10.3 bp per turn, result in an alignment of major and minor grooves from one superhelical gyre to the next. The resulting narrow channels formed by the aligned minor grooves serve as the exit points for four of the eight basic histone tails, whereas the large pores formed by the aligned major grooves are, in principle, free to make base-specific contacts with other proteins (**Figure 3**). Over 75% of the total DNA surface (29 000 $Å^2$) is exposed to solvent on the outside of the nucleosome. The dynamic (or static) disorder for DNA backbone atoms varies greatly, as is shown by the experimentally low crystallographic B-factors for those phosphates in direct contact with the histone octamer, and high B-factors for those facing away from it. This observation contradicts previous models of nucleosomal DNA being essentially rigid and inflexible.

The unexpected high flexibility of nucleosomal DNA is inherent in the design of the nucleosome, and is probably an important factor in its biological function. In addition, the nonuniform distortion of the DNA superhelix shows that not all regions of the DNA facing the solvent have

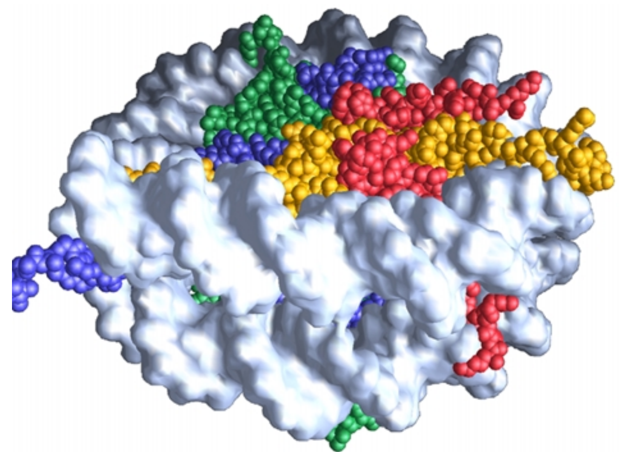

Figure 3 The nucleosome core particle in a 'space-filling' representation, in which each atom of the histone proteins (coloured as in **Figures 1** and **2**) is shown as a sphere. The DNA is represented by its molecular surface. This side view emphasizes the alignment of the grooves of the DNA across the two gyres of the DNA superhelix, and shows how the histone tails emerge from narrow channels formed by two minor grooves.

identical properties. For example, regions of highest curvature serve as the preferred point of action for human immunodeficiency virus (HIV) integrase *in vivo*.

Nucleosome positioning

On a long piece of DNA, a histone octamer may attain random positions, or it may prefer a particular translational and/or rotational position. Accurate translational positioning means that each histone octamer protects the same 147 base pairs of DNA on a longer fragment. Rotational positioning implies a preference for one face of the DNA to be contacted by the histone octamer. These two phenomena need not necessarily be connected.

The rules that underlie these positioning effects are not well understood. Translational positioning probably depends on how the DNA structure inherent to the sequence matches the local variations in the DNA curvature and helical periodicity in a nucleosome. Rotational positioning *in vitro* is likely to be a result of inherent anisotropic bending moments of the DNA. In simple terms, the histone octamer seeks the 'path of least resistance' when forming a nucleosome, occupying first the sites where the required energy for distortion is minimal. Positioning *in vivo* may additionally be influenced by the presence of prebound factors that exclude the formation of nucleosomes.

Although the majority of nucleosomes in a cell are randomly distributed, positioned nucleosomes over promoter regions or on repetitive DNA sequences are likely to fulfil a regulatory role, in that they may present or occlude transcription factor binding sites in a position-dependent manner.

Nucleosome dynamics

Analysis of nucleosome positioning *in vitro* and *in vivo* is complicated by the fact that the majority of nucleosomes are highly dynamic. The histone octamer is rarely maintained in a fixed position on the DNA; rather, it can slide and relocate over significant distances in a dynamic manner, thus enhancing the accessibility of DNA sequences that might be completely inaccessible in a static nucleosome. However, the molecular mechanism by which the histone octamer is relocated is still unknown. *In vitro* and *in vivo*, temperature-dependent sliding occurs without dissociation of histones from the DNA. *In vivo*, many ATP-dependent chromatin remodelling factors are thought to use their common catalytic subunit, an ATPase termed ISWI, to enhance the mobility of nucleosomes by an as yet unknown mechanism. The action of these remodelling factors is highly regulated and is targeted to specific sites by transcriptional activators.

Histone Variants

The core histone proteins of the nucleosome core particle have generally maintained an extremely high degree of conservation during evolution, emphasizing their central role in the compaction of DNA. The histone genes are present in multiple copies in most organisms, ranging from about 10- to 20-fold in mouse to several hundredfold in sea urchin, allowing for a certain degree of nonallelic variation. Sequence variance is by no means uniform among histone types. Histone H4 is almost immune to variation, whereas variants of other core histones are numerous, with H2A showing the greatest variability. All eukaryotic organisms contain such specialized histone protein variants with distinctly different amino acid sequences and expression patterns. Often, these histone variants are even more conserved among different species than the major core histones, suggesting that they fulfil a distinct role that cannot be adopted by 'regular', replication-dependent histone proteins.

Histone variant H2A.Z

One variant of histone H2A, H2A.Z, was recently shown to be essential for survival of different organisms including *Drosophila*, *Tetrahymena* and mouse. H2A.Z may play a pivotal role in initiating complex differential gene expression patterns and is preferentially associated with actively transcribed chromatin. Sequence comparisons indicate that there were two types of H2A genes in primitive eukaryotes before the divergence of the major eukaryotic groups, and that the major and variant H2As have been under different selective pressures since that time. The recently determined crystal structure of a nucleosome core particle containing H2A.Z suggests that the unique and essential function of H2A.Z is due to a combination of effects resulting from the destabilization of the histone octamer and from the specific binding of nuclear proteins to the altered nucleosomal surface.

MacroH2A and Cenp A

Other histone variants, for example macroH2A, and the H3 variant Cenp A, are associated with specialized chromatin structures. MacroH2A forms a core histone protein family with a hybrid structure consisting of a domain with high homology to histone H2A followed by a large nonhistone domain. MacroH2A1.2 is concentrated in the inactive X-chromosome in adult female mammals; its accumulation appears to be the earliest marker of the inactive X-chromosome. The inactive X-chromosome is perhaps the most dramatic example of specialized chromatin structure, in that it involves an entire chromosome, and it is exciting to speculate that this specialization starts at the nucleosomal level. Cenp A is an essential histone H3

variant that is located exclusively in nucleosomes at the centromere. These specialized nucleosomes appear to be involved in building the kinetochore.

It is completely unknown how these and other histone variants are targeted to their respective locations. Targeting may occur by the temporal separation of synthesis from that of replication-dependent core histones, as suggested for H2A.Z and Cenp A. Alternatively, the histone variants may be escorted by specialized, yet to be identified chromatin assembly factors.

Linker Histones

Native bulk chromatin is characterized by regular arrays of nucleosomes with defined internucleosomal distances. The nucleosome repeat length (the sum of the invariable length of 147 base pairs that are organized by the histone octamer, and the linker DNA) is not a constant but varies between species and cell types, during differentiation and during gene activation. However, it is not clear how this repeat length is determined and maintained in the cell.

The linker histone H1 is associated with the linker DNA as well as with the nucleosome core particle itself, and thus plays an important role in the compaction of DNA beyond the nucleosomal level. In the presence of H1, an additional 15–20 base pairs of nucleosomal DNA are protected against digestion with micrococcal nuclease. Analysis of native chromatin has shown that H1 exists in approximately stoichiometric amounts compared with the nucleosome core particle.

H1 function

Linker histones H1 and H5 have long been thought to be essential for chromatin condensation into higher order structures. However, recent experiments have challenged this dogma. Knockout experiments in *Tetrahymena* and *Aspergillus nidulans* show that H1, in contrast to the four core histone proteins, is not essential for nuclear assembly or cell viability, and reveal a much more subtle role for H1. Instead of acting as a general transcriptional repressor, H1 is found to regulate a limited number of specific genes. Surprisingly, H1 can both activate and repress transcription. Because the presence of linker histone H1 stabilizes the nucleosome by reducing histone octamer sliding and repositioning, removal of H1 may be used as a means to locally increase nucleosome mobility to control gene expression in either a positive or negative manner. *In vitro*, H1 depleted oligo-nucleosomes can fold to approximately the same compactness as in the presence of H1.

Despite these newer studies challenging the role of linker histones, it is clear that they stabilize nucleosomes, prevent nucleosome sliding, and assist the formation of higher order structure. In addition, the presence of H1 in all eukaryotes (with the possible exception of yeast), and its high degree of sequence conservation makes it likely that H1 plays an important, yet to be re-defined, role in chromatin organization.

H1 structure and its location on the nucleosome

Metazoan linker histones consist of a central globular 'winged helix' domain, a fold that has also been found in the DNA-binding domain of some transcription factors. Linker histones also contain long basic N- and C-terminal tails that are probably unstructured. *In vitro* studies have shown that the globular domain binds to the nucleosome, whereas the basic tails are thought to neutralize the negative charge of the linker DNA to allow further compaction. In addition, direct contacts are also made with the core histone H2A.

The high-resolution structures of the globular, tail-less domains of linker histones H1 and the variant H5 has been determined; however, neither one of these structures includes DNA. It is therefore not known how these proteins bind to nucleosomal and linker DNA. *In vitro* binding studies suggest that linker histones do not exhibit sequence specific-binding to DNA.

Careful analysis of binding stoichiometry and cross-linking experiments led to the conclusion that one H1 molecule binds close to the nucleosomal dyad (**Figure 1a**). However, conflicting results exist in the literature regarding its precise location. In addition, the role of its flexible tails in DNA binding and chromatin organization is far from clear. Depending on the degree of compaction, DNA sequence and chromatin context, and on the presence of other abundant nonhistone proteins, H1 might not occupy a unique position on a nucleosome, and the structure and position of the H1 tails might be especially variable. Final clarification of these important questions will have to await the crystal structure of the nucleosome core particle in complex with H1. Due to the reason given above, this has been extremely difficult.

Higher Order Chromatin Structure

The organization into nucleosomal arrays (10-nm fibre) only results in a 5-fold compaction of DNA. It is evident that even in the interphase nucleus, where chromatin is at its most approachable, significant compaction beyond the 10-nm fibre must occur. The next level of compaction is the 30-nm fibre, which involves the close packing of nucleosomes and which appears to be stabilized by the core histone tails and by H1. Even at this stage of compaction there is not enough space in the nucleus to accommodate the entire genome of higher eukaryotes, and it is thought

that regions of 10- and 30-nm fibres are exposed only locally and transiently.

The architecture of the 30-nm fibre has remained elusive even at low resolution. This is in part due to experimental difficulties in preparing large quantities of defined chromatin fibres *in vitro*, and in part due to a lack of methods that can yield high-resolution structural data of this highly complex superstructure. Chromatin fibres are most likely flexible and dynamic, and might interchange between different folded states. The population of these states can depend on many factors, such as the presence of other chromosomal nonhistone proteins, the modification state of core histones and linker histones, the position of the linker histone on the nucleosome, and internucleosomal spacing. These multiple sources for heterogeneity make the chromatin fibre an extremely difficult substrate to study by X-ray crystallography.

Some of these difficulties may be overcome in the near future by the availability of recombinant chromatin assembly systems that may be used to prepare evenly spaced nucleosomal arrays and higher order structures, using DNA sequences that position the histone octamer with a high accuracy. Additional advances will come from developments in X-ray crystallography, cryoelectron microscopy and other visualization methods.

Transcription in a Chromatin Context

The organization of DNA into nucleosomes and into higher order structure has an overall inhibitory effect on all cellular processes involving transcription. The active role of chromatin structure in transcription regulation is currently under intense investigation in many centres around the world, and involves, on the chromatin side, the study of histone modification pathways, chromatin remodelling factors, and histone variants.

Transcription initiation and elongation

A promoter must be nucleosome-free to allow complete assembly of the large RNA polymerase preinitiation complex. However, the molecular basis for the involvement of chromatin structure in recruiting transcription factors, and in aiding the first stages of assembly of the RNA polymerase preinitiation complex is not well understood, nor is it known to what extent nucleosomes inhibit the progress of the transcribing polymerase. The fact that many co-activators have HAT activity suggests that early stages of transcription activation involve the formation of alternative chromatin structure via the reversible acetylation of lysine residues in histone tails. It might be more than a coincidence that some components of the RNA polymerase preinitiation complex contain the histone fold.

Given the sheer size of many eukaryotic genes, it is unlikely that an entire gene will be ‘unpacked’ to allow the unhindered progress of the polymerase. What indeed happens if an ‘irresistible force’ (the advancing RNA polymerase) meets an ‘immovable object’ (the nucleosome)? Again, there is probably no simple solution to this problem; however, different centres are beginning to accumulate evidence about the fate of the nucleosome during transcription. Elegant *in vitro* experiments suggest that the polymerase may ‘step around’ a nucleosome without dissociating it from the DNA. Biochemical approaches have identified a factor that facilitates transcription through chromatin by competing for the (H2A–H2B) dimer and removing it from the nucleosome.

Outlook

Chromatin has made a remarkable transition from being viewed as ‘dead weight’ in the path of the DNA and RNA polymerases, to the realization that it plays a highly active role in regulating the expression of genes and DNA repair processes. Progress in this field can now only come from the joined forces of molecular biologists, biochemists and biophysicists to obtain a complete picture of transcription regulation in a native context. Biophysicists and structural biologists will have to provide a detailed picture of the different levels of higher order structure, whereas biochemists and molecular biologists need to untangle the intricate network that links chromatin with the transcription machinery.

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