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Structures and Functions of Chromatin Fibers

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Abstract

In eukaryotes, genomic DNA is packaged into chromatin in the nucleus. The accessibility of DNA is dependent on the chromatin structure and dynamics, which essentially control DNA-related processes, including transcription, DNA replication, and repair. All of the factors that affect the structure and dynamics of nucleosomes, the nucleosome–nucleosome interaction interfaces, and the binding of linker histones or other chromatin-binding proteins need to be considered to understand the organization and function of chromatin fibers. In this review, we provide a summary of recent progress on 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 diseases.

Contents

1. INTRODUCTION

The genomic DNA in eukaryotic cells wraps around a histone octamer to form a nucleosome, the basic unit of chromatin. In the presence of linker histones, nucleosomes in the array interact with each other to form a compact 30-nm fiber, typically regarded as the secondary structure of chromatin, which is further organized into higher-order chromatin structures. The chromatin architecture creates a huge barrier for DNA access in all DNA-related processes, including gene transcription, DNA replication, and repair. To achieve physical access to DNA, chromatin undergoes highly dynamical regulation by various factors such as histone modifications or variants, chromatin remodelers, and histone chaperons. In this review, we elucidate the recent progress on the structure and dynamics of chromatin fibers and discuss their related biological functions and abnormal organization in diseases.

2. NUCLEOSOME CORE PARTICLE: THE STRUCTURAL UNIT OF CHROMATIN FIBERS

The nucleosome consists of a nucleosome core particle (NCP) flanked by various lengths of linker DNA. The NCP contains a histone octamer around which 147 base pairs (bp) of DNA are wrapped approximately 1.7 times in a left-handed manner (72). The four highly conserved core histones (H2A, H2B, H3, and H4), which share a similar structure containing a histone fold region and a flexible N-terminal tail, form the octamer using two pairs of H2A/H2B dimers and one H3/H4 tetramer (4). In the nucleosome, each H2A/H2B dimer contacts the H3/H4 tetramer by way of a four-helix bundle formed between H2B and H4 and via the interaction between the H2A docking domain and the H3/H4 tetramer. The interaction between the two H2A/H2B dimers via the H2A-L1 loops further stabilizes the octamer (72).

The nucleosome structure is stable, with equilibrium constants (k_{eq}) of approximately 30 k_BT per 147 bp of DNA (98). Although the unwrapping of the entire nucleosomal DNA from the histone octamer is negligible, the nucleosome structure is intrinsically dynamic. The inherent

plasticity of the NCP has been examined using methyl-TROSY nuclear magnetic resonance (NMR) methods, which revealed alternative NCP conformations with significant dynamics at the central histone interface (63). Single-molecule Förster resonance energy transfer (FRET) studies revealed that the transient folding and unfolding dynamics of nucleosomal DNA happens in the timescale of milliseconds (64). Multiple highly dynamic modes including gaping, sliding, and breathing have been proposed (90). The mechanical unraveling of nucleosomes revealed that the outer and inner nucleosomal wraps present totally different mechanical responses, with the outer DNA wrap disassembled at a force of approximately 3 pN and the inner wrap disassembled at high tension up to 10 pN (85). These distinct mechanical properties are related to the organization of the histone octamer and its interaction with DNA, which are still important issues needing clarification. With a combination of FRET and optical tweezers, the asymmetric folding and unfolding behavior of the outer DNA wrap was further identified (91), which may help H2A/H2B dimers to be released sequentially (15). In addition, the H3/H4 tetrasome plays an important role in nucleosome assembly and nucleosome chirality. Investigation using freely orbiting magnetic tweezers (FOMT) showed that the H3/H4 tetrasome exhibits spontaneous hopping between the left-handed and right-handed states separated by 2.3 k_BT (129). Modification in the tetramer at the H3–H3 interface was found to enhance the formational plasticity of the tetrasome (96). The chirality choice of the tetrasome may provide a potential mechanism to regulate the DNA supercoiling property in the nucleus.

3. STRUCTURES OF CHROMATIN FIBERS: SOLENOID AND ZIGZAG

The method by which the nucleosome array folds into a condensed 30-nm fiber remains elusive. Two basic models have been proposed: the solenoid model and the zigzag model (81, 121, 134). The solenoid model suggests that nucleosomes are arranged linearly in a one-start solenoid-type helix with adjacent nucleosomes connected by a bend linker DNA (81). In the zigzag model, nucleosomes zigzag back and forth with relatively straight DNA linkers in a two-start stack pattern of nucleosomes (**Figure 1*a***, *right*) (121, 134). The latter model can be further divided into the helical ribbon model (134) and the twisted crossed-linker model (121). To discriminate among the models, high-resolution structures of chromatin fibers need to be resolved.

The chromatin in vitro reconstitution system has been well developed to improve the reproducibility and uniformity of chromatin fibers by using regular tandem repeats of unique nucleosome-positioning 601 DNA sequences and purified histone proteins (27). Using the reconstitution system, Richmond and colleagues (27) observed the two-row zigzag ribbon conformation on long nucleosomal arrays in the presence of Mg^{2+} or linker histone H1. Furthermore, they successfully resolved the crystal structure of tetra-nucleosomes with a nucleosome repeat length (NRL) of 167 bp at 120 mM Mg^{2+}, revealing two stacks of nucleosomes with the zigzag conformation (113). Strong interactions between the H2B-α1/αC and the H2A-α2 on the adjacent nucleosomes stabilize each stack of nucleosomes. More recently, the crystal structure of the tetranucleosome, with a shorter NRL of 157 bp, was solved; it is also compatible with the zigzag model but has different nucleosome face-to-face interactions (31).

Linker histones have been found to be essential for 30-nm fiber formation based on early electron microscopy (EM) studies on native chromatin (125). Rhodes and colleagues (110) found that both the linker histone and the NRL play critical roles in the formation of chromatin fibers. They reconstituted chromatin fibers under native conditions with a wide range of NRLs (from 177 to 237 bp) and in the presence of the linker histone and 1.6 mM Mg^{2+}, and they proposed an alternative solenoid structure (104). However, the 3D cryo-EM structures of chromatin fibers reconstituted from 12 or 24 nucleosomal arrays with different NRLs (177 or 187 bp) at 11 Å reveal

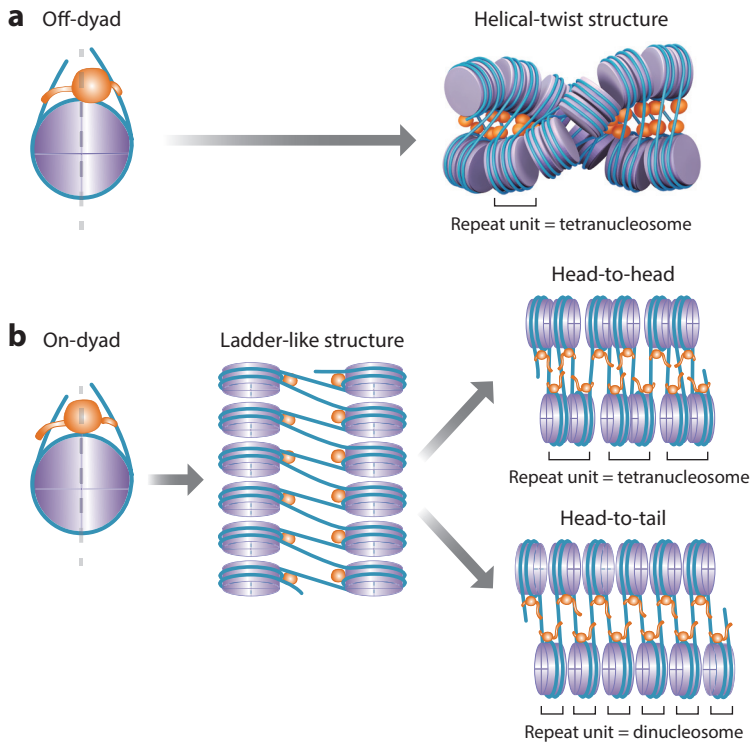

Figure 1

The localization of linker histones on nucleosomes may influence the assembly of the chromatin fiber. (*a*) The off-dyad binding of linker histones on nucleosomes in the helical-twist structure with repeating tetranucleosomal units (120). (*b*) The on-dyad binding of linker histones on nucleosomes in the flat ladder-like structure (44). The asymmetric arrangement of the N- and C-terminal tails of linker histone on the dyad of the nucleosome confers to the nucleosome a polarity that can be either head or tail, which results in two hypothetical arrangements of the chromatin fiber, one with repeating units of tetranucleosomes (*upper right*) and one with repeating units of dinucleosomes (*lower right*) (6). The dashed lines on the nucleosomes (*left*) indicate the nucleosome dyad axis.

a left-handed double helix twisted with the repeating tetranucleosomal units (120) (**Figure 1*a***, *right*). The four nucleosomes within the structural unit zigzag back and forth to form two stacks of nucleosomes, which appear to be very similar to the resolved X-ray structure of tetranucleosomes (113). The tetranucleosomal units are then twisted against each other in a left-handed manner to form the final helical structure. Single-molecular magnetic tweezer analysis further supports the existence of tetranucleosomal units (69). Under tension, the chromatin fiber unfolds first to an extended tetranucleosomes-on-a-string structure and then to a more relaxed beads-on-a-string conformation. Further increasing the force causes nucleosome unwrapping with two-step disruptions of the outer and inner DNA wrap (69). Importantly, similar dynamic processes were observed in chromatin fibers assembled on scrambled DNA sequence, suggesting that the existence of tetranucleosomal units is not dependent on DNA sequence (69).

Two types of nucleosome interface interactions (type I and II) have been found in the cryo-EM double helical twist structure (120) (**Figure 2**). Within the tetranucleosomal units, strong interactions between the H2B-α1/αC and the adjacent H2A-α2 (type I interaction) stabilize each stack of

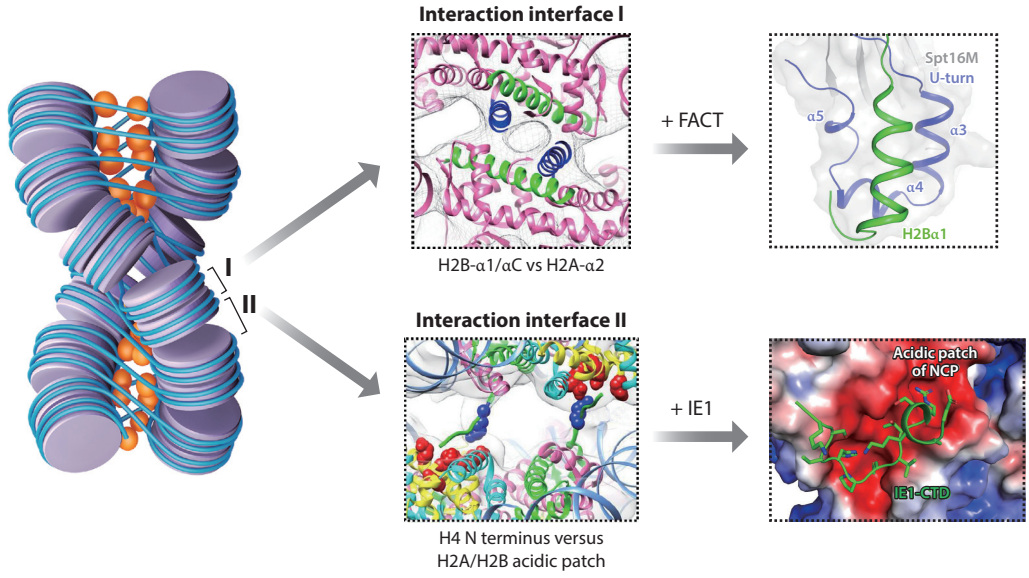

Figure 2

Two types of nucleosome interface interactions (type I and II) are revealed by the cryo-EM double helical twist structure (120). Within the tetranucleosomal units, strong interactions between the H2B-α1/αC and the adjacent H2A-α2 (type I interaction) stabilize each stack of nucleosomes; FACT recognizes the H2A/H2B dimer at the H2B-α1 to remodel the higher-order chromatin structure by interfering with the type I interaction (69). The interactions of the H4 N-terminal tail with the neighboring H2A/H2B acidic patch (type II interaction) stabilize the interaction interface between tetranucleosomal units; IE1-CTD binds at the H2A/H2B acidic patch to impair the compaction of chromatin fibers by interfering with the type II interaction (37). Abbreviations: CTD, C-terminal domain; EM, electron microscopy; IE1, immediately early 1; NCP, nucleosome core particle.

nucleosomes, as revealed by the resolved X-ray structure of the tetranucleosome (113). Between the tetranucleosomal units, the interactions of the H4 N-terminal tail with the adjacent H2A/H2B acidic patch (type II interaction) and the H1–H1 interaction play central roles. These two interfaces may provide two distinct regulation platforms for different chromatin factors, such as histone modifications or variants, histone chaperons, and other architectural proteins. The tetranucleosome may provide an additional level of gene regulation beyond the nucleosome, and it has been postulated to be a structural and functional unit of the genome. Notably, the low energy required to disrupt the type II interaction (approximately 1.8 k_BT) (69), which is comparable to the thermal fluctuations, suggests that chromatin fibers may undergo spontaneously rapid folding or unfolding dynamics between a compact regular 30-nm fiber and an extended tetranucleosomes-on-a-string structure at physiological conditions in vivo.

More recently, the crystal structure of an H1-bound hexanucleosome with NRL of 187 bp has been resolved with 9.7-Å resolution, which also reveals a two-start zigzag conformation but with a flat ladder-like organization without twist (44) (**Figure 1*b***). Only a uniform nucleosomal stacking interface, being similar to the type II interface in the helical twist structure, was observed. The nucleosome packing density of the flat structure is only half that of the twisted fiber. In addition, a mild change in ionic environment shifted the flat conformation to a more compact twisted form. The results suggest that the untwisted form represents a plausible intermediate during the assembly of condensed chromatin fibers. The diversity of structures in response to different local environments provides insights into the conformational plasticity of chromatin fibers in vitro.

4. THE ROLES OF LINKER HISTONES IN CHROMATIN FIBERS

The structure of the linker histone includes three domains, a short N-terminal domain (NTD), a globular domain, and a long intrinsically disordered C-terminal domain (CTD) (2). The globular domain is highly conserved, with approximately 80 amino acids, and has a winged helix structure (58). The NTD and CTD have been shown to behave as intrinsically disordered regions, which may fold on binding to DNA (107), and the CTD has been shown to be a major determinant of binding of H1 and consequent folding of chromatin fibers (71).

Multiple redundant linker histone variants exist in many metazoans. In humans and mice, 11 linker histone variants have been indentified, including seven somatic subtypes (H1.1 to H1.5, H1.0, and H1.10) and four germ line–specific subtypes [H1.6 (TS), H1.7 (TS), H1.8 (oo) and H1.6 (TS)] (55). Linker histones are also subjected to complicated posttranslational modifications (PTMs), including phosphorylation, methylation, and acetylation, which may change the secondary structure of the CTD or the binding of linker histone with DNA or other proteins to modify the structure and function of chromatin (108). For instance, the methylation of H1.4-Lys26 helps to recruit HP1 to promote the formation of heterochromatin (21), while the acetylation of H1.4-Lys34 has been found to be related to transcriptional activation (57). During the cell cycle, the S/TPXK/R motifs in the CTD of H1 can be phosphorylated by serine kinases, which play an important role in the regulation of chromatin compaction (1). In addition, several PTMs have been identified on the global domain of linker histone H1.1–H1.5, many of which occur on the residues involved in interactions with DNA and are predicted to destabilize the H1–nucleosome complex (132). The PTMs of linker histones are often subtype specific, which adds a new layer of complexity to subtype differences. It will be of great interest to investigate the functions of different H1 variants and their PTMs in the formation of chromatin fibers at the atomic resolution.

It is generally acknowledged that linker histone binds to approximately 10 bp of linker DNA to form a stem-like structure at the entry and exit sites of the NCP. To illustrate how linker histone binds to the nucleosome, two main models have been proposed, the on-dyad (symmetrical) and the off-dyad (asymmetrical) models (**Figure 1**). In the on-dyad model, the globular domain is located symmetrically on the dyad axis, whereas in the off-dyad model, the globular domain is displaced from the dyad axis and binds the nucleosome asymmetrically (6, 120, 142, 143) (**Figure 1*a*,*b***, *left*). The linker histone H1.4 in the double helical twist structure shown by cryo-EM interacts with both the dyad and entering or exiting DNA of the nucleosome in a three-contact mode, with the globular domain binding the nucleosome core in an apparently off-dyad mode (120) (**Figure 1*a***, *left*). In contrast, Bai and colleagues (143) solved the crystal structure of the globular domain of H5 bound to a 167-bp nucleosome at near atomic resolution, showing an obvious on-dyad binding mode (**Figure 1*b***, *left*). However, an NMR study from the same group showed an off-dyad binding mode for the globular domain of *Drosophila* H1 (142). Recently, the cryo-EM structure of a 197-bp nucleosome complexed with H1.0 showed on-dyad binding of the globular domain, with the CTD primarily binding to a single linker DNA to disrupt the twofold symmetry of the nucleosome (6). These studies suggest that the binding model of linker histone with the nucleosome may change with different H1 isoforms. Alternatively, given that the on-dyad binding of H1/H5 was all observed in the nucleosome particle, and the off-dyad binding was mainly found in the chromatin fiber, it is likely that the globular domains of linker histone may switch from an on-dyad location to an off-dyad location during the folding of higher-order chromatin structures (34).

In addition, the asymmetric arrangement of the N- and C-terminal tails of H1 to the dyad of the nucleosome, as revealed by earlier biochemical and recent structural studies (112, 120), may

confer on the nucleosome a polarity that can be either head or tail. Such polarity of the H1-bound nucleosome may significantly influence the formation of higher-order chromatin structures (6), as shown in **Figure 1*b*** (*right*). Indeed, the cryo-EM double helical twist structure shows that, within a tetranucleosomal unit, the two adjacent stacked nucleosomes are arranged with the opposite polarity to that of the H1 location (120). This specific arrangement of H1 polarity within the tetranucleosomal unit yields a different spatial arrangement and distribution of CTD-bound linkers, which consequently results in the H1–H1 association between tetranucleosomal units. The dimerized linker histones within the fiber are more constrained and can thus stabilize the coherent stacking and twisting of the tetranucleosomal units (120). Alternatively, the nucleosomal array can fold into an untwisted flat fiber with the dinucleosome as the structural unit, in which the two adjacent stacked nucleosomes are arranged with the tandem polarity of the H1 location (**Figure 1*b***).

5. THE STRUCTURAL POLYMORPHISMS OF CHROMATIN FIBERS

5.1. Histone Variants and Chromatin Fibers

The incorporation and replacement of histone variants create architecturally distinct chromatin states and play diverse functions in genome-associated biological processes. Histone variant H2A.Z is found throughout most eukaryotic lineages and shares approximately 60% similarity in sequence with canonical H2A. The high-resolution structure of H2A.Z-NCP reveals an extended acidic patch domain on the surface of the NCP compared to canonical nucleosomes, which may provide a specific, larger docking domain for nucleosome-binding proteins and nucleosome–nucleosome interactions (122). The incorporation of histone variant H2A.Z not only stabilizes the nucleosome structure, but also facilitates the compaction of nucleosomal arrays into a featured flat ladder-like chromatin fiber and promotes HP1α-mediated chromatin fiber folding (14, 34).

Histone variant H3.3 differs from canonical H3 by only four amino acid residues, three of which are hidden inside the NCP in region 87–90 and one of which, residue Ser31, is exposed outside of the NCP. The four–amino acid difference does not affect the nucleosome stability, but does greatly impair the chromatin compaction (14). Both H2A.Z and H3.3 prefer to localize at nucleosomes flanking gene promoters and transcriptional start sites and may coordinate to regulate chromatin features for gene regulation (13, 14, 131). The incorporation of H3.3 does not affect the stabilization effect of H2A.Z on nucleosome structure, but does counteract H2A.Z-mediated chromatin compaction and antagonize the inhibitory effects of H2A.Z on chromatin transcription by RNA Pol II (14). In addition, H2A.Z and H3.3 function cooperatively to establish featured chromatin structures at the enhancer and promoter regions of RAR/RXR-targeted genes and help to recruit the ATP-dependent chromatin remodeling complexes and/or histone-modifying enzymes to remodel the nucleosome structure upon gene induction (14, 68). Although H3.3 is deposited in transcriptionally activated chromatin fractions by the UBN1/UBN2-HIRA complex, recent studies have shown that H3.3 is incorporated at transcriptionally inactive heterochromatin regions of the genome, such as the telomere and pericentric regions, by the H3.3-specific chaperones DAXX and ATRX (29, 46). It will be of great interest to investigate how all of the components coordinate with each other to form the transcriptionally inactive heterochromatin structures.

The centromere-specific histone H3 variant (CenH3, termed CENP-A in humans) is incorporated into the centromeric chromatin and functions as an epigenetic marker essential for centromere identity and function (3). In human cells, CENP-A is specifically recognized and deposited into centromeres by HJURP (30, 39). Structural and biochemical analyses have identified the CATD of CENP-A as the exclusive region responsible for HJURP binding (5, 10), and the

residue Ser68 also plays an essential role in HJURP recognition (54). The dynamic phosphorylation or dephosphorylation of Ser68 in CENP-A, mediated by the Cdk1/Cyclin B and PP1α complexes, temporally controls the HJURP-mediated assembly of CENP-A into centromeric regions (137). The crystal structure of the CENP-A nucleosome reveals that the αN helix of CENP-A is markedly shortened as compared to that of canonical H3, which weakens the interactions with DNA at the entry and exit sites (123). The results suggest that the DNA ends of the CENP-A nucleosome are partially unwrapped and become flexible. The flexible DNA ends of the CENP-A nucleosome are required for centromere function; CENP-A mutants with H3-αN, which wraps the DNA ends more tightly in the nucleosome, are significantly defective (109). Binding of CENP-C helps to reshape and stabilize the CENP-A nucleosomes at the centromere (33). In addition, structural comparison of the CENP-A and H3 nucleosomes revealed that the RG loop, composed of the extra two CENP-A-specific residues Arg80 and Gly81 in loop1, is specifically located at the lateral surface and exposed to the solvent (123). Further investigation demonstrated that the exposed RG loop not only provides the recognition site for the binding of CENP-N, but also facilitates the folding of CENP-A nucleosomal arrays into a compact ladder-like structure in the presence of Mg^{2+} (36). This structure inhibits the binding and recruitment of CENP-N by hiding the RG loop within CENP-A chromatin fibers. The dynamic switch from a compact to an open chromatin state due to the dilution of the CENP-A nucleosome enables the exposed RG loop to recruit CENP-N at the S phase (36).

5.2. Linker DNA Lengths and Chromatin Fibers

The length of linker DNA is one of the most important internal factors known to affect the structure of chromatin fibers. EM measurements have revealed that a short NRL (167 bp) results in a clear zigzag topology, whereas a medium-length NRL (197 bp) forms highly compact solenoid structures (104). A cryo-EM study revealed that chromatin fibers with NRLs of 177 or 187 bp form helical twist fibers with a zigzag conformation (120). In contrast to the constant length used in these structural studies, the NRLs in native chromatins are highly variable. It is still obscure whether the NRLs of the fibers are discrete units or change continuously, since analysis of NRLs by micrococcal nuclease (MNase) digestion rarely provides a resolution higher than ±4 bp. It is extremely difficult to obtain high-resolution structures for chromatin with such heterogeneous NRLs, but computational modeling has focused primarily on the length and local geometry of linker DNA, as well as the effect of electrostatic internucleosomal interactions on the structure of chromatin fibers (24, 133). These studies have shown that the twist angle of nucleosomes along the DNA plays an important role in determining the straight-linker superhelical structure. The nucleosome prefers to be oriented with its symmetry axes parallel to the fiber axis for repeat lengths that are integer multiples of the DNA pitch, and with perpendicular axes for half-integer multiples of the pitch. Extended structures are formed for repeat lengths close to an integer multiple of pitch, with much shorter fibers of near half-integer multiples (65). Most recently, the effect of a wide range of intrafiber NRL variations in chromatin structure was explored through Monte Carlo simulations of the mesoscale chromatin model, which suggested a wide range of different architectures (highly bent narrow forms, canonical and irregular zigzag fibers, and polymorphic conformations) depending on the NRLs that were mixed together (18).

Crystal structural studies have indicated that the NCP has a rigid structure, with a well-defined path of 147-bp nucleosomal DNA. An addition of 1 bp to linker DNA changes the orientation of the nucleosome by approximately 36° with respect to its adjacent neighbors. Recent experiments have shown that small NRL deviations (±2 and ±4 bp from the mean repeat) do not significantly change the compaction of chromatin (19, 104), which indicates that the intrinsic chromatin

fiber must allow for different NRLs and accommodate a noninteger periodicity of the DNA helix (10.5 bp/turn). To avoid the high energy costs of rotating the nucleosomes to their preferred angle in chromatin fibers, nucleosomes may change their entry or exit DNA geometry in vivo through partial unwrapping of nucleosomes by acetylation of histone tails (77), introduction of histone variants such as CENP-A (123) and H2A.Bbd (28), or the action of nucleosome remodeling complexes (59). Drastic alternation of the nucleosome geometry might also occur if nucleosomes dissociate into hemisomes, as reported for *Drosophila* centromeric nucleosomes (20). In addition, EM experiments showed that a short stem was observed on the linker DNA of the nucleosome (7). It is not clear whether the size of the stem is constant or depends on the NRL or the type of linker histone bound. The globular domain of H1 has been shown to play important roles in maintaining the orientation of nucleosome discs relative to the fiber axis (75). Thus, geometrical considerations of the fiber should allow for some differences of the actual distances between the consecutive nucleosomes.

5.3. Non-Histone Architectural Proteins and Chromatin Fibers

Structural analyses of chromatin fibers clearly imply that two important interaction interfaces (type I and II) in the 30-nm fiber could potentially be regulated by different chromatin binding proteins (44, 113, 120) (**Figure 2**). The FACT complex, a conserved histone chaperone for H2A/H2B dimers, has been shown to destabilize nucleosomes for RNA polymerase progression on chromatin templates and maintain chromatin integrity in vivo (8, 40). Recently, a structural study revealed that FACT recognizes the H2A/H2B dimer at the H2B-α1, involved in the type I interaction interface of chromatin fibers, by the U-turn motif of Spt16M (50) (**Figure 2**). A single-molecular study demonstrated that FACT can remodel higher-order chromatin structures by interfering with type I interaction and destabilizing the tetranucleosomal unit (69). More importantly, genomic analyses showed that FACT may destabilize the N/N + 2 micro-C interactions (i.e., the tetranucleosomal motifs) to facilitate gene transcription in yeast (69). Other chromatin binding proteins that recognize the type I interaction interface, such as INO80, which recognizes H2B-αC (126), may also fulfill their biological functions via interfering with type I interactions to modulate the structure and dynamics of chromatin fibers.

The H2A/H2B acidic patch and the H4 N-terminal tail located in the type II interaction interfaces also provide important anchoring sites for many nucleosome-binding proteins to affect the chromatin structures. Several nonhistone binding proteins costructured with the nucleosome have been shown to interact with nucleosomes via the acidic patches, including immediately early 1 (IE1) (37), RCC1 (76), CENP-C (60), and PRC1 (82). The human cytomegalovirus IE1 protein has been found to associate with condensed host chromatin during mitosis, mainly via its chromatin-tethering domain located at the CTD (IE1-CTD, amino acids 476 to 491) (118). The crystal structure of NCP in complex with IE1-CTD demonstrates that the IE1-CTD is well positioned in the acidic patch of the nucleosome (37) (**Figure 2**). The specific binding of IE1-CTD at the acidic patch impairs the compaction of higher-order chromatin structures (37). Interestingly, this chromatin-modulating activity is not shared by another acidic patch–binding viral protein, LANA, suggesting that distinct modes of protein binding to the acidic patch could exert different influences on chromatin structures. Different modifications of the H4 N-terminal tail not only directly interfere with type II interactions, but also provide important anchoring sites for nucleosome-binding proteins to regulate chromatin structures. It has been shown that mono- and dimethylated H4K20 recruit the malignant brain tumor (MBT) protein L3MBTL1 to compact nucleosomal arrays, which results in negative regulation of the expression of a subset of E2F target genes (127).

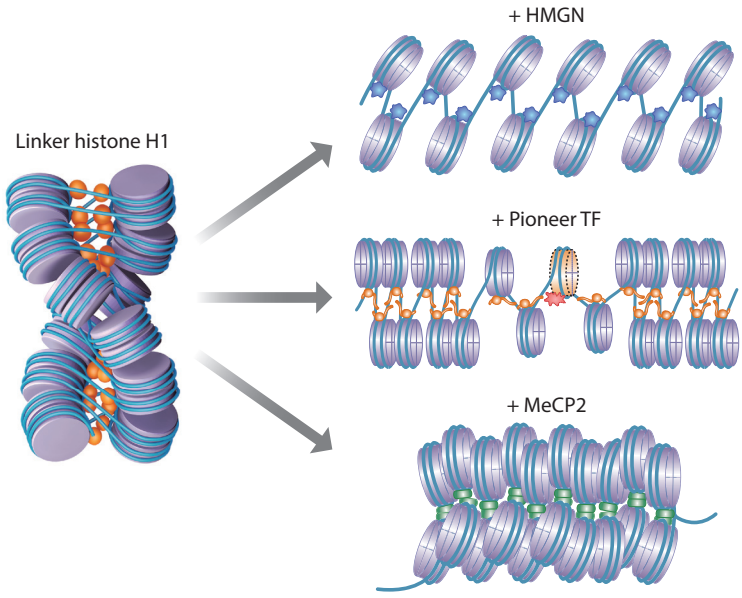

Figure 3

Many nonhistone chromatin proteins regulate chromatin structures by interfering or competing with the binding of H1 on chromatins. HMGN proteins overlap with the binding location of H1 on the nucleosome to counteract the linker histone–mediated chromatin compaction and facilitate transcriptional activation (106). Pioneer transcription factors (TFs) recognize their binding sites in H1-compacted chromatin to open the local chromatin or nucleosome domain (16). Methyl CpG binding protein 2 (MeCP2) competes with H1 for chromatin binding sites and induces chromatin compaction in a different manner (45).

Many nonhistone chromatin proteins regulate the chromatin structurers by interfering or competing with the binding of H1 to chromatins (**Figure 3**). The high mobility group (HMG) proteins have been shown to promote chromatin decompaction and enhance the accessibility of chromatin targets to regulatory factors (105). The HMG superfamily is composed of three families: HMGN, HMGB, and HMGA. All HMGN proteins specifically recognize the structure of the NCP and overlap the binding location of H1 on the nucleosome (99). In addition, a methyl-based NMR study on the HMGN2–nucleosome complex showed that the negatively charged CTD of HMGN2 is positioned near linker DNA to interfere with its interaction with H1, and HMGN2 can also interact with the H2A/H2B acidic patch to decondense the chromatin (61). Bustin and colleagues (106) demonstrated that the negatively charged CTD of HMGN5 interacts with the positively charged CTD of H5, thereby counteracting the linker histone–mediated compaction of chromatin to facilitate transcriptional activation, which is consistent with another recent report that HMGB1 interacts with linker histone H1 (11). In addition, methyl CpG binding protein 2 (MeCP2) is another chromatin binding protein that shares binding sites on nucleosomes with H1 (136). Mutations in MeCP2 cause neurodevelopmental alterations that account for more than 95% of Rett syndrome (RTT) cases (12). EM measurements showed that MeCP2 competes with H1 for chromatin binding sites and induces chromatin compaction by dramatically reducing the nucleosomal DNA entry and exit angles (45). It will be of great interest to investigate the high-resolution structure of the MeCP2-chromatin fiber to understand how MeCP2 mutants may result in abnormal organization of chromatin fibers in a diseased state.

6. CHROMATIN FIBERS IN NUCLEUS

Structural studies in vitro revealed that the 30-nm fiber exhibits a left-handed helical structure twisted by tetranucleosomal units (113, 120). However, evidence for the existence of 30-nm chromatin fibers in vivo has been controversial. Early cryo-EM studies showed that chromatin fibers are indeed the most predominant forms of starfish sperm and nucleated chicken erythrocyte chromatin (51). Using cryo-EM tomography of vitreous sections, Frangakis and colleagues (114) showed that the most predominant form of chromatin in chicken erythrocyte nuclei is chromatin fibers arranged in a two-start helix formation with the nucleosomes juxtaposed face to face by approximately 6.7 nucleosomes per turn. The stacked nucleosomes were shown to be shifted off the superhelical axes with an axial translation of approximately 3.4 nm and an azimuthal rotation of approximately 54°, results that agree well with the high-resolution structure of in vitro reconstituted chromatin fibers (113, 120). During the past 20 years, chromosome conformation capture (3C)-based genomic approaches for mapping chromatin interactions, such as Hi-C and ChIA-PET, have yielded genome-wide chromatin interaction maps at unprecedented resolution (22, 41, 70). Limited by the resolution of Hi-C data, even the most precise Hi-C (kilobase resolution) cannot provide detailed information for the 30-nm fiber in vivo (95). However, a few recent studies have mapped local chromatin folding at nucleosome resolution by Micro-C genomics or imaging approaches, providing support for a tri- or tetranucleosome motif in yeast (52, 94) and extended two-start helical fibers consisting of at least 2–3 tetranucleosomal stacks in mammalian cells (48, 53, 66). Using EM-assisted nucleosome interaction capture cross-linking experiments in combination with mesoscale modeling, Schlick and colleagues (48) showed a dominant relaxed two-start zigzag organization, rather than the longitudinal compaction usually associated with the 30-nm fiber. In addition, RICC-seq measuring fragment length distribution (FLD) of DNA strand breaks induced by ionizing radiation also supported the existence of 30-nm fiber structures in vivo that are spatially organized with the zigzag conformation (111). Most recently, Greenleaf and colleagues (103) provided the first genome-wide map of the chromatin secondary structure in living human cells at the 1–3 nucleosome (50–500 bp) scale using the RICC-seq technique. Unbiased analysis of RICC-seq signals in intact interphase nuclei reveals that H3K9me3- and H3K27me3-marked heterochromatin regions are consistent with variable longitudinal chromatin compaction of two-start helical fibers with face-to-face stacked alternating nucleosomes in tri- or tetranucleosome units, as seen in the structure of reconstituted chromatin fibers (120). Yang and colleagues (74) developed a novel 30-C model combining 30-nm chromatin structure models with Hi-C data, which measured the spatial contact frequency between different loci in the genome. Experimental data of ionizing radiation–induced FLD and yields of single-strand breaks (SSBs) and double-strand breaks (DSBs) were used to validate the 30-C model, which predicts that the most probable chromatin fiber structure for human interphase fibroblasts in vivo is 45% zigzag 30-nm fibers and 55% 10-nm fibers (74).

This overwhelming body of experimental evidence from EM and genomic studies strongly supports the idea that the two-start helical fiber with stacked alternating nucleosomes is an important mechanism for generating chromatin compaction both in vitro and in vivo. However, some cryo-EM, X-ray scattering, and electron spectroscopy imaging (ESI) studies of the nucleus do not support the existence of regular chromatin fibers in cells (42, 43, 93). Due to the poor contrast of DNA in vitreous ice and the limited 3D sampling volume of ESI, it is technically difficult to identify chromatin unambiguously and to reconstruct the 3D organization of chromatin via large nuclear volume in cryo-EM experiments. Recently, O'Shea and colleagues (97) developed a novel chromEMT technique by using electron microscopy tomography (EMT) to visualize the chromatin ultrastructure and the 3D organization across multiple scales in the nucleus. They found

that a minority of the chromatin (less than 20%) is made up of up to 30-nm fibers in human interphase and mitotic cells in situ, and most chromatin fibers make up a flexible and disordered granular chromatin chain with diameters between 5 and 24 nm. However, some important issues need to be clarified in this technique, including whether the DNA-binding fluorescent dye DRAQ5 binds to other types of nucleic acids in situ, such as RNA (particularly double-stranded RNA), and whether the DNA in compacted chromatin fragments is equally accessible for staining as the free DNA. In addition, extensive fixation by chemical cross-linking and dehydration by ethanol during sample preparation in chromEMT may damage the ultrastructure of the chromatin fiber. Therefore, it is still a challenge to preserve the natural 3D conformation of chromatin fibers in chromEMT or cryo-EM tomography.

7. BIOLOGICAL FUNCTIONS OF CHROMATIN FIBERS

7.1. Chromatin Fibers in Gene Transcription

Although it is believed that the interconversion between permissive and refractory chromatin structures is important in regulating gene transcription, this process is poorly understood. Recent genome-wide chromatin immunoprecipitation analyses indicated that not only the nucleosomes at promoter and enhancer regions but also the higher-order chromatin organization are highly dynamic (135). It is now clear that chromatin structure exhibits a highly dynamic equilibrium between an open conformation exemplified by the beads-on-a-string structure and a compact 30-nm fiber. To address the roles of higher-order chromatin dynamics in transcriptional activation, an in vitro system was developed to reconstitute highly compacted 30-nm chromatin fibers using RSF/NAP-1 (68); this demonstrated that linker histone H1 and deacetylation of core histones are required for formation of 30-nm fiber, which is refractory to transcription by RNAP II. Recently, advanced microscopic studies indicated that transcriptionally inactive genomic regions contain higher H1 densities and denser chromatin clusters than do transcriptionally active regions (102). Transcription from H1-bound chromatin is elicited by the H1 chaperone NAP1, which is recruited in a gene-specific manner through direct interactions with activator-bound p300 that facilitate core histone acetylation and concomitant eviction of H1 and H2A/H2B (117). Chromatin compaction by H1 has long been thought to repress transcription by restricting transcription factor interactions, but whether chromatin compaction is sufficient to preclude factor association and how the repression is reversed have not been clear. The HMG and PARP1 proteins, which compete with H1 to bind nucleosomes in vitro and/or mutually exclusive genomic occupancies (67, 100), and ATP-dependent chromatin remodelers and histone chaperones have been shown to promote transcription from H1-bound chromatin templates in vitro (68, 139). H1 eviction has also been reported for transcriptional activation by retinoic acid and progesterone receptors, which are apparent pioneer factors capable of recognizing binding sites in H1-compacted chromatin (68, 128).

Pioneer transcription factors, which can bind nucleosomal DNA to enable gene expression from regions of the genome with closed chromatin, are required for stem-cell pluripotency, cell differentiation, and cell reprogramming (128). Pioneer factors FoxA and GATA-4 have been shown to recognize their binding sites in H1-compacted chromatin, leading to the opening of the local nucleosomal domain in the absence of ATP-dependent enzymes (16). The ability of FoxA to open chromatin is mediated through its DNA-binding domain, which competes with the globular domain of H1 and its CTD, which binds histone H3 and H4 (16, 17). The recent cryo-EM structure of DNA-binding domains of Sox2- and Sox11-bound nucleosomes showed that SOX factors can bind and locally distort DNA at superhelical location 2 and facilitate detachment of the nucleosomal DNA from the histone octamer to increase DNA accessibility (26). Sox-factor

binding to the nucleosome can also lead to a repositioning of the N-terminal tail of H4, which mediates the nucleosome stacking by interacting with the H2A/H2B acidic patch of the neighboring nucleosomes (72, 120). In addition, the cryo-EM structure of OCT4-SOX2-bound nucleosomes showed that OCT4-SOX2 can locally distort the nucleosomal DNA or remove DNA from the histone H2A/H3 in nucleosomes, depending on its motif location (84). Recent single-molecule fluorescence studies found that Rap1 can bind nucleosomal DNA within a chromatin fiber, thus opening the structure by inhibiting internucleosome contacts (86). These studies show that pioneer factors are sufficient to access and open local chromatin structures for the binding of other activators that cannot bind to the nucleosomal template. However, it is not clear how the pioneer factor can target its DNA sites in the context of higher-order chromatin structures to affect the local chromatin state.

7.2. Chromatin Fibers in Epigenetic Inheritance

Epigenetic inheritance is defined as heritable information on chromatin that is not encoded in the DNA sequence and that is essential for cell fate specification in multicellular organisms (62). During cell division, the chromatin states must be faithfully inherited to the appropriate loci of each daughter DNA molecule. Following DNA replication, recycled parental histones with specific histone PTMs and newly synthesized histones are assembled into nascent chromatin behind the replication fork, which leads to an at least twofold dilution of the epigenetic information, and must be properly restored to their original states to maintain a unique cell identity (56, 62). A recent study showed that parental nucleosomes from repressive, but not active, chromatin domains are redeposited within the same chromatin domains after DNA replication, indicating that the inheritance of a repressive chromatin domain is preferred over that of the active state (32). The repressive histone PTMs, including H3K9me3 catalyzed by Suv39h1/h2, H3K27me3 catalyzed by PRC2, and H4K16 deacetylated by the Sir complex, have been shown to mediate a heritable chromatin state (79, 101). The enzymes, including Suv39h1/h2 and PRC2, exhibit a positive feedback read-and-write model in which a given modification from parental nucleosomes recruits chromatin modulators that contain both the histone-binding module and the enzymatic activity to propagate the mark on the newly assembled nucleosomes (80).

Beyond the read-and-write model, higher-order chromatin structures also play important roles in the inheritance of a repressive chromatin state (124) (**Figure 4**). In silico modeling of epigenetic inheritance suggested that the inheritance of chromatin states via histone proteins is poorly transmitted when the positive feedback loop is limited to adjacent nucleosomes (25). Experimental evidence, such as the evidence of reduction of H3K27me3 by H1c/d/e-TKO, stimulation of PRC2 activity by H1 or dense chromatin, and propagation of H3K27me3 enhanced by long-range contacts of chromatin (35, 138), supports this conception. Notably, a recent investigation showed that the H1-compacted chromatin fiber enhances the long-distance propagation of H2AK119ub1 and thereby reinforces the inheritance of H2AK119ub1 by RYBP-PRC1 through a nucleosome–nucleosome pairing mechanism during the cell cycle (140). Either disruption of RYBP-PRC1 activity or impairment of higher-order chromatin structures by triple-knockout of H1c/d/e resulted in severe defects of the establishment and inheritance of H2AK119ub1, as well as the neural differentiation of mouse embryonic stem cells (140).

7.3. Abnormal Chromatin Fibers in Diseases

Given the regulatory role of chromatin for all DNA-related processes, it is not surprising that the chromatin itself or the protein machineries that write, read, and erase the histone PTMs are

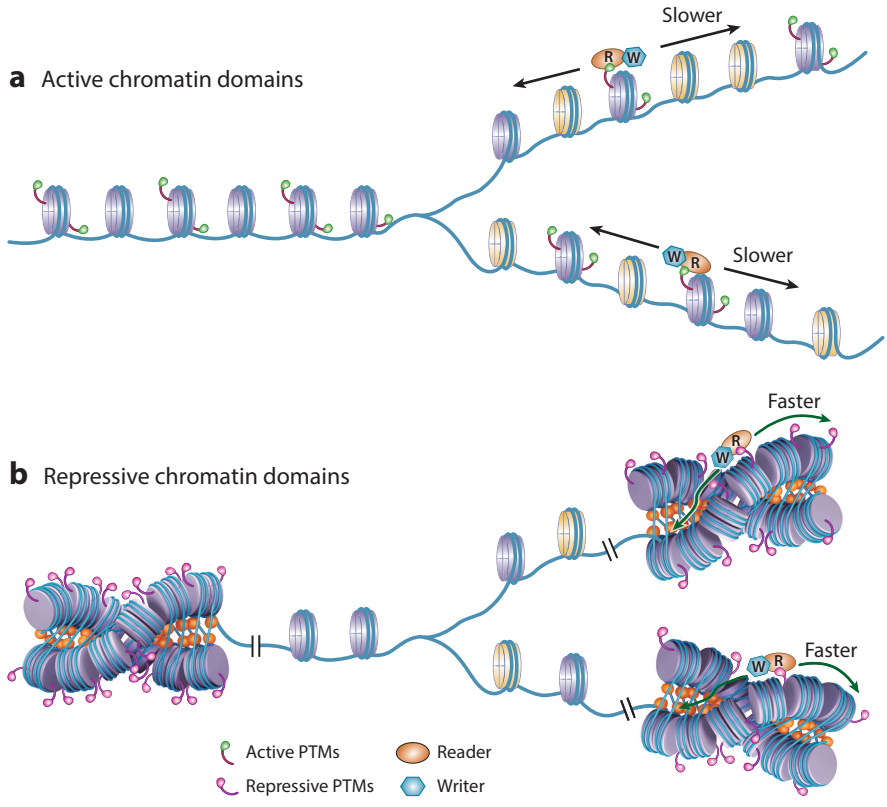

Figure 4

Chromatin fibers in epigenetic inheritance. (*a*) At the active chromatin domains, the positive feedback loop is not efficiently or slowly established during cell division. (*b*) The compact chromatin fibers at repressive heterochromatin bring the neighboring nucleosomes closer by nucleosome–nucleosome pairing and promote the propagation of the repressive posttranslational modifications (PTMs) to daughter cells through a positive feedback read-and-write model (32, 140).

frequently mutated in cancers, many of which are oncogenic drivers or contribute to tumor progression (116). Mutations in the histones have been linked to cancers; for example, mutations in histone H3/H3.3, including K27M and G34V/R, occur with high genetic penetrance within rare pediatric gliomas and sarcomas (115). These mutations, some of which act in a dominant fashion, have been deemed oncohistones. The locations of these oncohistone mutations are at or near key PTMs in the histone tails, suggesting that these mutations might disrupt the reading, writing, and/or erasing of these marks. Recently, Allis and colleagues (87) showed that somatic histone mutations occur in approximately 4% (at a conservative estimate) of diverse tumor types and in crucial regions of histone proteins. Interestingly, they found that mutations occur in all four core histones, not only at or near residues that contain important PTMs but also at sites that are unlikely to affect PTMs, including sites within the histone fold domain. Notably, four out of five of the most mutated residues are in globular domains, i.e., E105 of H3, E76 of H2B, E97 of H3, or E113 of H2B, which are not expected to affect PTMs. In addition, mutations on the H2A/H2B acidic patch at residues E113 of H2B and E92 and E56 of H2A occur at high frequencies (87), which may impair the chromatin higher-order organization. The H2B-E76K substitution was also observed to be the most common mutation in an independent study by Bennett and colleagues (9)

and has been shown to disrupt the interaction between H2A/H2B and H3/H4 to destabilize the nucleosome and make chromatin more sensitive to MNase digestion. H2A-E56K/Q mutations were previously reported in human uterine and ovarian carcinosarcomas (141) and have also been reported in non-small-cell lung cancer, renal cell carcinoma, small-cell lung cancer, and others. The frequently occurring mutations in the core histones in cancer may represent a new mechanism of epigenetic dysfunction that involves destabilization of nucleosomes and chromatin fibers, leading to deregulation of chromatin accessibility and alteration of gene expression to drive cellular transformation (83).

Notably, the genetic aberration of HIST1H1E was found to associate with the transformation of follicular lymphoma to diffuse large B-cell lymphoma (47). Massive parallel sequencing analyses identified HIST1H1E as one of the 10 most frequently mutated genes in primary cutaneous diffuse large B-cell lymphoma, leg type (78). In addition, frameshift mutations affecting the C-terminal tail of HIST1H1E have been causally linked to Rahman syndrome, a recently recognized developmental disorder characterized by mild to severe intellectual disability, a distinctive facial gestalt, variable somatic overgrowth, and an aging appearance (38). HIST1H1E encodes the ubiquitously expressed human linker histone H1.4. In the presence of H1.4, nucleosome arrays arrange into a twisted left-handed double helix with a zigzag two-start tetranucleosome (120). The C-terminal tail of H1.4, which has an abundance of lysine residues, has been found to be important for stable folding of nucleosome arrays into chromatin fibers and is required for high-affinity binding to chromatin in vivo (49). It will be of great interest to investigate whether these mutations in H1.4 disrupt proper chromatin compaction and function to cause or contribute to the development of related diseases.

MeCP2 was originally identified as a transcriptional repressor that recognizes and binds preferentially to methylated CpG dinucleotides flanked by AT-rich segments (88). Clinical genetics studies showed that RTT mutations predominantly locate in two discrete regions of MeCP2, MBD and TRD (23). A classic model has been proposed in which MeCP2 represses gene transcription mainly by interacting with DNA methylation via MBD and recruiting HDAC-containing corepressor complexes by TRD, interactions that are affected by RTT-associated missense mutations (73, 89). Both in vitro and in vivo studies have revealed an inverse correlation between MeCP2 and H1 in chromatin binding, chromatin compaction, and higher-order chromatin organization (88, 92). MeCP2 deficiency results in a doubling of H1 levels and global changes of chromatin organization in neurons, which suggests that MeCP2 serves as an alternative chromatin architecture protein (119). A recent investigation showed that MeCP2 and H1 can compete with each other in phase separation of chromatin to form mutually exclusive droplets with distinct properties, which suggests that, in neurons, H1 and MeCP2 may bind to distinct genomic regions and organize the genome into distinct heterochromatin domains (130). It will be of great interest to investigate the structural details of the MeCP2-bound chromatin fiber and determine whether the mutations in MeCP2 disrupt proper chromatin compaction and function to cause or contribute to the development of RTT.

8. PERSPECTIVES AND CONCLUSIONS

Recent high-resolution structural analyses of chromatin fibers have provided the fundamental structural features necessary to understand the basic principles of chromatin compaction. With the aid of linker histone H1, nucleosomes have been found to interact with each other via two types of interaction interfaces to form compact zigzag chromatin fibers. Some chromatin-related proteins, for example, FACT and IE1 proteins, may fulfill their biological functions via interfering with type I or II interactions to modulate the structure and dynamics of chromatin fibers. Many

nonhistone chromatin proteins, including MeCP2, HMG proteins, and pioneer transcription factors, regulate the structure of chromatin fibers by interfering or competing with the binding of H1 on chromatins. It will be of interest to investigate whether other interaction interfaces between nucleosomes and other forms of chromatin structures exist in different conditions, for example, in the presence of other chromatin architectural proteins or with different histone variants or NRLs. The 3D organization of chromatin fibers in situ still needs to be further investigated using advanced and newly developed techniques, including genomic approaches (such as micro-C and RICC-seq) and CRISPR-based imaging techniques. In addition, mutations on the components of chromatin fibers, including the core histones, linker histones, and MeCP2, have been frequently found to be oncogenic drivers or contribute to the disease progression of cancers and neuronal disorders. Further investigations into the structural basis and dynamic regulation of chromatin fibers in vitro and in situ will enhance our understanding not only of the diversity of chromatin structures in vivo, but also of the regulation of chromatin fibers to fulfill their biological functions in genomic DNA and their abnormal functioning in related diseases.

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