Minireview

Keeping fingers crossed: heterochromatin spreading through interdigitation of nucleosome arrays

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Abstract Interphase eukaryotic nuclei contain diffuse euchromatin and condensed heterochromatin. Current textbook models suggest that chromatin condensation occurs via accordion-type compaction of nucleosome zigzag chains. Recent studies have revealed several structural aspects that distinguish the highly compact state of condensed heterochromatin. These include an extensive lateral self-association of chromatin fibers, prominent nucleosome linker 'stems', and special protein factors that promote chromatin self-association. Here I review the molecular and structural determinants of chromatin compaction and discuss how heterochromatin spreading may be mediated by lateral self-association of zigzag nucleosome arrays.

Key words: Heterochromatin; Nucleosome; Histone; Higher order folding; Chromatin 3D structure

1. Introduction

In eukaryotic cells, chromatin is packed through a hierarchy of folding levels. The basic packing level is represented by an array of uniform repeating units, the nucleosomes. Each nucleosome has a core of 146 bp of DNA making about 1.7 superhelical turns around an octamer of four pairs of core histones, H2A, H2B, H3, and H4; the nucleosome core crystal structure is now solved at atomic resolution [1]. When isolated in solution of low ionic strength, the nucleosomes are seen as 'beads-on-a-string' arrays where the nucleosome core 'beads' are connected by 20–80 bp of linker DNA 'strings'. Further compaction of nucleosome arrays in chromatin fibers is achieved through the higher order chromatin folding. The predominant form of higher order chromatin seen in vitro is a fiber of 30 nm diameter. Current textbook models depict the 30 nm fiber as a zigzag nucleosome array capable of accordion-type longitudinal folding that could underlie chromatin compaction in vivo [2].

Chromatin is most condensed in metaphase chromosomes during mitosis or meiosis and decondensed in the interphase between the cell divisions. However, even in the interphase the chromatin packing is not even and two morphologically different types of chromatin can be distinguished: the dispersed euchromatin and the condensed heterochromatin [3,4]. Heterochromatin becomes especially abundant in the nuclei of terminally differentiated cells where the majority of formerly active genes are repressed and condensed [5]. Although it has been long proposed that heterochromatin formation involves significant structural changes that could interfere with transcriptional activation and other DNA-dependent processes (see e.g. [6–8]), the precise structural changes in DNA folding upon condensation of repressed chromatin have remained obscure.

This work summarizes the recent advances in understanding the higher order chromatin structure and proposes a new mode of chromatin condensation through inter-fiber bridging between zigzag nucleosome arrays that may explain the intricate mechanism of developmentally regulated heterochromatin formation and spreading.

2. Basics of chromatin higher order folding: the 30 nm fiber and linker DNA stems

In vitro studies of isolated nucleosomal arrays provided most of the current information on higher order chromatin structure. Using transmission electron microscopy Thoma et al. [9] first demonstrated that at low concentrations of monovalent salts, nucleosome arrays adopt a zigzag conformation where extended linker DNA is located in the middle and nucleosome cores are located at the periphery of the chromatin fiber. Further advancement of imaging techniques has shown that the 30 nm fiber is neither regular nor symmetric, linkers are not supercoiled, and most of the nucleosomes are not engaged in close contacts either in vitro [10,11] or in situ [12]. To explain the consistent diameter of the chromatin fiber, the 3D zigzag model allows a high degree of variation in nucleosome-to-nucleosome rotation angle β (Fig. 1a) consistent with variable DNA linker length. An irregular 3D zigzag that incorporates natural linker length variability of ± 2–3 bp closely resembles 30 nm fibers observed by transmission electron microscopy [10], atomic force microscopy [11], and cryo-electron microscopy [13].

The 3D zigzag model predicts that in a compact chromatin fiber, linker DNA remains relatively straight and the entry/exit angle α (Fig. 1a) becomes low. The nature of this transition was uncovered using cryo-electron microscopy of ice-vitrified oligo- and polynucleosomes [13,14] and transmission electron microscopy of reconstituted unfixed mononucleosomes [15]. Both imaging techniques have shown that nucle-

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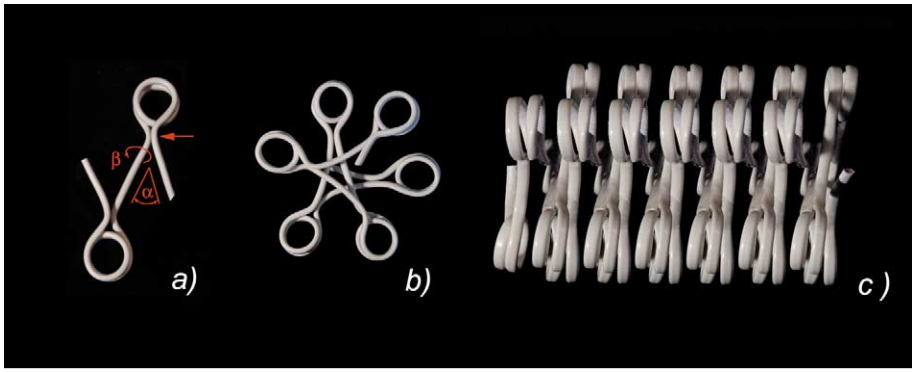

Fig. 1. Compaction of a nucleosome zigzag chain into a 30 nm fiber. a: Model of a dinucleosome zigzag repeating unit showing nucleosome linker entry/exit angle α, the nucleosome rotation angle β, and linker DNA stem (arrow). b,c: Cross-section view (b) and side view (c) of a compact form of zigzag chromatin fiber with parallel orientation of nucleosome cores.

osome linkers enter and exit the nucleosome at a very small angle forming an intersection zone about 8 nm from the nucleosome center (arrow in Fig. 1a). This linker 'stem' extends for 3–5 nm after which the linkers diverge. The nucleosome linker stem mediates nucleosome arrays folding into compact 30 nm fibers with centrally located linkers and nucleosome cores staying at the periphery (Fig. 1b, also compare with electron microscopy in Fig. 2a–h). A recent Monte Carlo modeling of irregular nucleosome zigzag with linker stems resulted in the prediction of chromatin fiber diameter and mass per unit length [16] that is in excellent agreement with earlier experimental values [17]. The 3D zigzag model is also consistent with single molecule experiments that used optical tweezers to measure elastic force required to extend a chromatin fiber [18–20].

Linker histones (histone H1 and related proteins) play a pivotal role in higher order folding of 30 nm fibers [9] by stabilizing the compact chromatin conformation [21]. Histone H1 has a unique protein organization with a central globular domain and extended positively charged C- and N-terminal domains. Within a nucleosome, the linker histone globular domain is located near the nucleosome dyad axis at the linker entry/exit site [22]. This location together with the ability of the globular domain to bind simultaneously two separate DNA molecules [23] are neatly consistent with the role of histone H1 in the linker DNA stem formation.

A new line of evidence suggests that the C-terminal linker histone domain, previously thought to be quite unstructured, contributes to linker stem formation. Bharath et al. noticed a striking sequence homology between the C-terminal domain of histone H1 and HMG box fold motif and predicted that, like HMG box proteins, the C-terminal domain could induce DNA bending [24]. By placing the globular domain at its previously determined binding site at the nucleosome dyad axis, the authors position the C-terminal domain at the site where the two linkers come into close contact by making inward kinks and then diverge [25]. The authors propose that the C-terminal domain contributes to the stem extension and thus defines the path of linker DNA inside chromatin.

The local DNA concentration in 3D zigzag fibers as predicted for randomly oriented nucleosome cores (0.04–0.14 g/ml) is considerably less than the one predicted for the most compact form of chromatin such as 0.17 g/ml in metaphase chromosomes [26,27]. This is also true for the most condensed interphase heterochromatin. For example, differentiated mouse erythroid FVA cells contain abundant heterochromatin and acquire the nuclear diameter of 4 μm [28] with a DNA concentration of 0.18 g/ml. To explain the high DNA concentration, Daban et al. suggested that chromatin might form a very compact regular solenoid where nucleosome cores form tight parallel stacks [27]. The discovery of high rotational flexibility in linker stems [29] suggests that nucleosome orientations may fluctuate. Such fluctuation would allow a zigzag with initially irregular nucleosomes to adopt a more regular and compact folding (Fig. 1c) consistent with the high local DNA concentration in condensed chromatin.

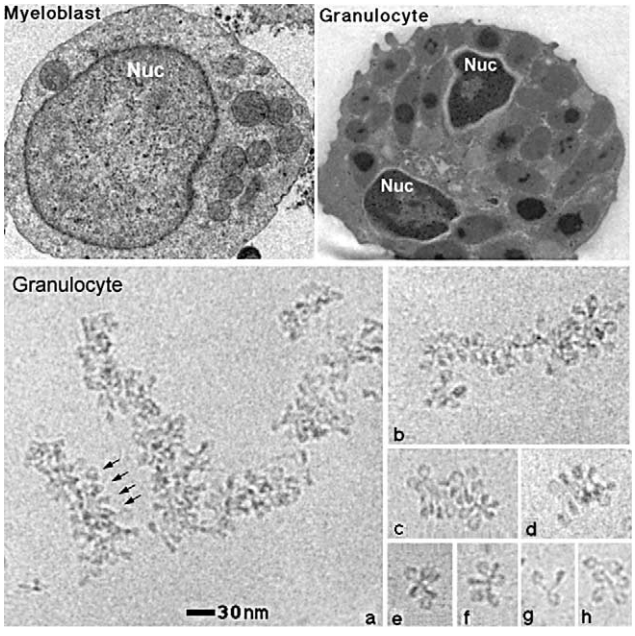

Fig. 2. Electron microscopy of heterochromatin in situ and in vitro. Top panels: Transmission electron microscopy of ultrathin cell sections shows a sharp contrast between the decondensed chromatin of undifferentiated chicken myeloblast (left) and condensed chromatin in the terminally differentiated granulocyte (right). Bottom panels: Cryo-electron microscopy of unfixed unstained polynucleosomes isolated from chicken granulocytes and vitrified in a 20 mM ionic strength buffer. a: Long granulocyte polynucleosomes comprising highly compact chromatin fibers. Note separate nucleosome disks stretched out at the periphery of self-associated chromatin (arrows). b–h: Smaller and less compact poly- and oligonucleosomes from the same sample. Reprinted with permission from [35].

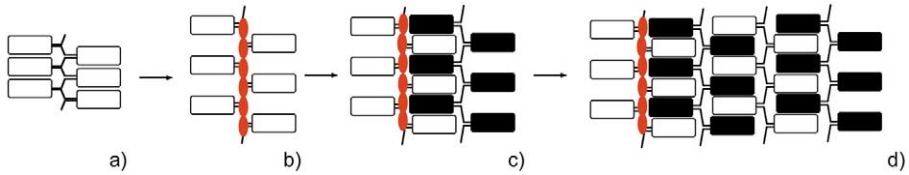

Fig. 3. A model for heterochromatin spreading by interdigitation of zigzag nucleosome arrays. Upon interaction with a chromatin-condensing factor (red ovals), a compact 30 nm fiber (a) is stretched (b) and then interacts with another 30 nm fiber to make a self-associated structure (c). Lateral fiber interdigitation stretches out the nucleosomes cores at the edge of the self-associated structure and may promote further self-association (d) even in the absence of additional chromatin-condensing factors.

3. Chromatin compaction through intercalation of chromatin fibers

Does chromatin condensation in the nuclei involve the compaction of 30 nm fiber such as shown in Fig. 1c? Electron microscopic imaging and computer-mediated tomography of a starfish, *Patiria miniata*, sperm chromatin resulted in distinct 30 nm fibers showing irregular asymmetric arrays of separate nucleosomes highly consistent with the irregular zigzag model [12]. However, this well distinguished organization of the sperm chromatin is an exception rather than a rule. Most other cell types with extensive heterochromatin visualized using similar techniques showed highly convoluted masses of chromatin rather than distinct fibers. Woodcock and Horowitz who studied *Patiria* chromatin along with many other types of chromatin concluded that extensive lateral association and intercalation of nucleosome arrays may explain the absence of distinct chromatin fibers in many types of condensed chromatin in situ [30].

To visualize long-range chromatin transitions using fluorescent microscopy techniques, Belmont and his colleagues constructed long (hundreds to thousands kb) DNA segments ontaining multiple repeats of lac operator DNA and introduced them into the genome of CHO cells. In situ electron microscopy of an extended artificial chromatin domain aided by immunogold labeling with antibodies against the lac repressor fusion protein revealed chromatin fibers with a diameter of 80–100 nm, significantly higher than in the 30 nm fibers observed in vitro [31]. In condensed metaphase chromosomes distinct structures of 250 nm diameter but no 30 nm fibers have been observed [32]. Thus, although details of the chromatin folding in situ remain obscure, most ultrastructural experiments suggest that the 30 nm fiber is not a universal form of higher order structure in situ and the nucleosome arrays form some more extensively folded or bridged structures.

In many types of terminally differentiated cells, e.g. in granulocytes shown in Fig. 2 (top right panel), most of the nuclear chromatin turns into condensed heterochromatin. Several ultrastructural studies of such chromatin revealed thick chromatin fibers (diameter 45–50 nm) apparently resulting from folding back and partial interdigitation of 30 nm chromatin fibers [33,34]. Among several types of condensed chromatin, polynucleosomes isolated from chicken granulocytes retained the most compact folding in low ionic strength solutions and thus provided the highest resolution for cryo-electron microscopy [35]. Fig. 2 shows chromatin derived from granulocyte nuclei featuring thick (45–50 nm) electron-dense structures apparently originating from the folding of a chromatin 30 nm fiber back on itself (panels a–c). The foldback structure diameter is less than expected for two 30 nm fibers lying side by side (60 nm) indicating that the chromatin folding involves mutual intercalation of nucleosomes between the laterally interacting fibers. Other distinct features of the condensed chromatin are the separate nucleosome disks seen at the periphery of the self-associated fibers that form no contacts with each other (arrows in Fig. 2a) and the prominent linker DNA stems seen in smaller, less convoluted particles (Fig. 2c–h).

4. Heterochromatin proteins that promote chromatin bridging

The abrupt increase of chromatin self-association linked to heterochromatin formation appeals for understanding which heterochromatin-associated factors bring about this transition. Recent studies have shown that MeCP2, a protein that binds methylated DNA and heterochromatin, causes extensive compaction and self-association of biochemically defined nucleosome arrays in vitro [36]. The interactions of MeCP2 with chromatin (which are very important for understanding the molecular basis of MeCP2 mutations linked to Rett syndrome [37]) are most likely to occur at a limited number of chromosomal loci involved in transcriptional regulation. HP1 (heterochromatin protein 1) has a more global role in promoting chromatin-mediated repression and heterochromatin spreading through direct interaction between di- and tri-methylated lysine 9 in histone H3 and the chromodomain of HP1 [38–40]. Its role as a factor causing chromatin bridging has been recently demonstrated in *Drosophila*, where HP1 tethered to certain loci on polytene chromosomes formed contacts with distant chromosomal sites [41]. Very recent works have shown that small non-coding RNA molecules cooperate with HP1-like proteins in heterochromatin spreading [42,43]. The RNA-induced silencing complexes may be essential structural components that not only initiate but also 'glue' spatially separate regions of heterochromatin together [44].

Nuclei of most vertebrate cells contain three isoforms of HP1: α, β, and γ [45]. Remarkably, interactions of one HP1 subtype, HP1α, with chromatin are primarily mediated not by its chromodomain but rather via interaction of the HP1 hinge region with DNA [46]. When interacting with chicken erythrocyte chromatin, HP1α recognizes and selectively binds to a heterochromatic fraction with longer DNA [46]. This chromatin fraction strikingly resembles the extensively self-associated 'A-particles' first isolated by Weintraub [47] which also contain longer DNA at the ends [48]. This peculiar mode of chromatin interaction makes HP1α a possible candidate to participate in chromatin bridging though its chromatin-condensing ability remains to be shown.

Surprisingly, all three HP1 subtypes are dramatically reduced in terminally differentiated avian erythrocytes [49] and erythrocytes from other non-mammal vertebrates [50] showing that heterochromatin can be condensed without HP1. In

chicken erythrocytes and granulocytes it is replaced by a developmentally regulated heterochromatin protein, MENT (myeloid and erythroid nuclear termination stage-specific protein) which binds 'A-particles' and interacts with histone H3 methylated at lysine 9 [49]. A molecular analysis of MENT has revealed a protein domain (RCL) essential for chromatin repression in vivo [51] as well as for nucleosome array bridging in vitro [52]. Strikingly, electron microscopy reveals a stronger folding of nucleosome arrays by a mutant with an inactive RCL than by wild-type MENT. This suggests that the folding and the bridging activities of MENT compete with each other, such that MENT folds more efficiently when its bridging activity is inactivated. On the basis of these experiments and the cryo-electron microscopy of MENT-compacted chromatin (Fig. 2a) it was proposed that MENT might connect intercalated zigzag nucleosome arrays by internal protein bridges leaving relatively open nucleosomes at the periphery of the fiber [52].

5. Heterochromatin spreading by antiparallel nucleosome interdigitation

Surprisingly, chromatin isolated from several cell types with abundant heterochromatin such as nucleated mouse erythroid cells [50,53] and lymphocytes [54] does not contain any prominent chromatin structural protein present at a level that might be sufficient for its condensation. It thus is conceivable that chromatin condensation can spread to the majority of chromatin without stoichiometric binding of additional chromatin-condensing proteins.

Here I propose that chromatin-condensing factors (red oval in Fig. 3) initiate chromatin condensation by stretching out the nucleosome disks on the outer side of a nucleosome zigzag (Fig. 3a,b) and thus promoting lateral interdigitation of zigzag nucleosome arrays (Fig. 3c). The interaction between nucleosome zigzags would be facilitated by anti-parallel nucleosome core stacking. The anti-parallel nucleosome interaction is consistent with crystal [55] and some semi-crystal [56] forms of the nucleosome core and especially with the face-to-face antiparallel nucleosome stacking revealed by X-ray crystallography of nucleosomes with chicken erythrocyte histones [57].

The zigzag organization of a nucleosome array provides a clue to how such interaction once primed may be spread even in the absence of the chromatin-condensing factors. Here the second zigzag strain after intercalation on one side of the zigzag will automatically have the nucleosomes on the other side of the zigzag stretched out (Fig. 3c) and poised for subsequent interdigitation (Fig. 3d). Although initially disordered, the nucleosome cores can rotate around their linker stems [29] allowing the nucleosome planes in the interacting fibers to align for optimal stacking. This extensively interdigitated structure would have a DNA concentration consistent with the most condensed forms of chromatin [27]. Progressing interdigitation may result in global chromatin condensation as observed in terminally differentiated cells (Fig. 2) leaving behind only the genes protected by boundary elements [58] or by nuclear matrix association [59]. These elements are known to fix the active chromatin in alternative subnuclear compartments thus physically disconnecting it from the masses of spreading heterochromatin.

The nucleosome array interdigitation (Fig. 3) implies that the nucleosome segment opposite the linker entry/exit site may be directly involved in stabilizing heterochromatin structure. Particularly interesting in this respect is the role of histone H2A variant, H2A.Z, which has the highest degree of sequence variation from canonical H2A in its L1 loop located at this segment [60]. H2A.Z blocks heterochromatin spreading in vivo [61] while in vitro it does not alter mononucleosome structure [62] but rather inhibits nucleosome array self-association [63] indicating that it may destabilize heterochromatin by disrupting contacts between intercalated nucleosome arrays.

There is a growing line of evidence showing that heterochromatin structure is much more dynamic than has been appreciated before. Thus, even the most condensed chromatin in terminally differentiated cells can be decondensed and reactivated in transient heterokaryons [64]. Furthermore, some genes located within heterochromatin or associated with heterochromatin-promoting factors are transcriptionally active thus complicating the functional definition of heterochromatin [65]. Consistent with the above findings (but still surprising) is the high in vivo mobility of heterochromatin-associated proteins such as linker histones [66,67], HP1 [68,69] and MENT (Grigoryev and Misteli, unpublished). The nucleosome interdigitation model (Fig. 3d) is nicely compatible with the dynamic 'breathing' of heterochromatin in vivo where a block of self-associated nucleosome arrays could accommodate transiently dissociated nucleosome interfaces. It is not so easy to tackle heterochromatin dynamics in vitro where chromatin self-association leads to its aggregation and insolubility. However, the identification of contact points between the intercalating nucleosomes and the sites of nucleosome interaction with chromatin-condensing factors that could be subsequently mutated and tested in vivo should provide new clues for the precise molecular mechanism of heterochromatin spreading. Such studies are currently in progress.

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