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On the role of inter-nucleosomal interactions and intrinsic nucleosome dynamics in chromatin function



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ABSTRACT

Evidence is emerging that many diseases result from defects in gene functions, which, in turn, depend on the local chromatin environment of a gene. However, it still remains not fully clear how chromatin activity code is 'translated' to the particular 'activating' or 'repressing' chromatin structural transition. Commonly, chromatin remodeling in vitro was studied using mononucleosomes as a model. However, recent data suggest that structural reorganization of a single mononucleosome is not equal to remodeling of a nucleosome particle under multinucleosomal content – such as, interaction of nucleosomes via flexible histone termini could significantly alter the mode (and the resulting products) of nucleosome structural transitions. It is becoming evident that a nucleosome array does not constitute just a 'polymer' of individual 'canonical' nucleosomes due to multiple inter-nucleosomal interactions which affect nucleosome dynamics and structure. It could be hypothesized, that inter-nucleosomal interactions could act in cooperation with nucleosome inherent dynamics to orchestrate DNA-based processes and promote formation and stabilization of highly-dynamic, accessible structure of a nucleosome array. In the proposed paper we would like to discuss the nucleosome dynamics within the chromatin fiber mainly as it pertains to the roles of the structural changes mediated by inter-nucleosomal interactions.

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1. Introduction

Most aspects of eukaryotic gene functions are tightly controlled by the programming of chromatin activity states – misregulations of this system result in malignancies including cancer, metabolic disorders, cardiovascular disease, diabetes, and a number of other diseases and behavioral pathologies [1–5]. To understand the role

of chromatin regulatory machinery and its components in specific disease states, it is important to clarify the molecular mechanisms of how chromatin activity 'code' is 'translated' to the particular 'activating' or 'repressing' structural transitions in chromatin.

The repeated basic unit of chromatin, the nucleosome (which is described at the near-atomic resolution [6,7]), in its 'canonical' form consists of 147 bp of DNA wrapped in 1.7 left-handed supercoils around an octamer of histone proteins (H3/H4 tetramer flanked on either side with a H2A/H2B dimer). Nucleosomes are

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connected in arrays by linker DNA of variable-length [8,9]. On further levels of compaction nucleosome chain folds into still debatable ‘helical’ solenoid [10–12] or ‘zig-zag’-like [13–15] superstructures to form the 25–34 nm fiber. Chromatin fiber is stabilized by linker histones H1/H5 [16], which promote the solenoid/zig-zag arrangement [9,17–20]. The 30 nm fiber further self-associates and condenses into higher-order tertiary structures.

The ‘canonical’ nucleosomes – stabilized by multitude protein-DNA and protein-protein interactions – restrict accessibility and dynamics of underlying DNA and inhibit DNA-based processes. The basic, not mutually exclusive, mechanisms alleviating nucleosome occlusion include: (i) reorganization of the nucleosome structure by enzymatic activities [21–23] and (ii) ‘alteration’ of nucleosomal histones by various posttranslational modifications (PTM) [24–26] or (iii) replacement of ‘canonical’ core histones by functionally-relevant histone variants [27–30] and their PTM species [28,31,32]. However, a growing attention is concentrated on the nucleosome-regulatory mechanisms that are based on the inherent features of canonical nucleosome structure – such as, the spontaneous fluctuations of nucleosomal compaction (‘nucleosome breathing’) and the regulatory effects of inter-nucleosomal interactions on the nucleosome structure and dynamics.

It is becoming evident that a nucleosome array (more correctly, a sequence of histone core octamers on the DNA) does not constitute merely a ‘polymer’ of individual ‘canonical’ nucleosomes due to multiple inter-nucleosomal interactions which affect nucleosome dynamics and structure. For instance, remodeling of a single mononucleosome is not equal to remodeling of a nucleosome in multinucleosomal context – interaction of nucleosomes via flexible histone termini could significantly alter the mode and resulting products of nucleosome structural transitions. Transient inter-nucleosomal interactions can also mediate distant communication in chromatin [33,34]. Hypothetically, inter-nucleosomal interactions could promote formation and stabilization of distinct, “active” structure of a nucleosome array. We would like to discuss these phenomena in view of the recent as well as older literature data.

2. Nucleosome-dimer and nucleosome-octamer particles and their biological implications

Decades ago it has been shown that a nucleosome can cooperatively associate with an additional histone octamer [35–40] or another nucleosome [35,38,41]. Such ‘nucleosome-octamers’ and ‘nucleosome-dimers’ are likely formed by similar mechanisms, which involve trans-interactions between histone octamers. A nucleosome can bind more than one additional histone octamer or a nucleosome with a weaker association constant [37,39] that could result in nucleosome multimers [41]. The precise structure of nucleosome-dimers/nucleosome-octamers is not fully clear, however it was presumed that the basic nucleosomal organization is preserved in these structures – such as, the nuclease protection pattern and the digestion kinetics were not significantly altered [37,42,43]. Although the formation of nucleosome-dimers/octamers is favored by elevated (0.2–0.6 M) NaCl, we note the mono- and dinucleosome propensity to self-associate at ‘physiological’ 100–120 mM NaCl in the presence of 1.5–2.5 mM MgCl₂ (unpublished observation). Interestingly, gel-purified mononucleosome-dimers tend to dissociate into individual mononucleosomes upon freezing-thawing at a –80 °C (unpublished).

It was estimated that about 25% of nucleosomes during assembly/refolding are involved in the nucleosome-octamer/dimer formation [37]. This suggests that nucleosome propensity to adsorb extra histones could be common in vivo and could be of biological significance – such as, play a role in transient chromatin

disassembly-reassembly during DNA replication or transcription. For instance, a nucleosome behind the RNA polymerase could transiently ‘adsorb’ a histone octamer (or its components, such as H2A/H2B dimers [40,44]) from the nucleosome ahead of the RNA polymerase (Fig. 6E). In this scenario the nucleosome can ‘survive’ during passage of the RNA polymerase and reinstate its original position on the DNA.

The nucleosome-dimer/octamer formation, likely, has common basis with the reversible self-association of nucleosomal arrays at elevated (above ~2 mM) concentrations of magnesium [45,46] (reviewed in [9,47]). Histone tails, which are intrinsically unstructured in unbound state, [6,48–50] protrude from the nucleosome surface and only insignificantly contribute to the conformation and stability of the compact nucleosome core [51–56]. However, the additive effect of histone tails is essential for oligonucleosome folding and oligomerization [53,57–59] with H4 and H3 tails making the major contribution [58–60]. Inter-nucleosomal interactions that control the salt- and magnesium-dependent polynucleosome folding have been extensively examined by site-directed histone-histone and histone-DNA crosslinking [61–66]. These studies revealed multitude interactions of histone termini between themselves and with DNA in an intra- and inter-nucleosomal manner (reviewed in [9,47]). For instance, the compaction of nucleosome arrays critically depends on the interactions of histone H4 termini with the basic patch on the surface of H2A/H2B dimer of a neighboring nucleosome [13,66–70].

3. Biological implications of inter-nucleosomal interactions

It could be supposed that inter-nucleosomal interactions involving histones termini are involved not only the in the chromatin higher-order formation. These interactions could give rise to formation of a histone tails ‘network’ extending over many nucleosomes. In cooperation with intrinsic nucleosome dynamics (see below), this network could have an essential role in regulating functional activity of nucleosome arrays. It is on note, that the ‘closed-pair’ nucleosome-nucleosome interactions, modulated by histone modifications, could play a role in nucleosome deposition and organization of nucleosome arrays [71]. Martin and colleagues [72] have shown that inter-nucleosomal interactions in di- and oligonucleosomes dramatically increase histone H3 methylation by the EZH2/EED complexes, which exhibited only minor enzymatic activity on the mononucleosomes [72] – in addition, remodeling of di- and oligonucleosomes (but not mononucleosomes) by incorporation of histone H1 further increased H3 methylation by EZH2 [72]. SET7 and ALL-1 SET-domain polypeptides showed binding preferences for dinucleosomes (but not mononucleosomes) which were remodeled with yeast ISW1/ISW2 [73]. Similarly, ISW2 remodeling of nucleosome-dimer particles facilitated their association with ALL-1 SET-domain [43]. Molecular bases of these phenomena are not yet clear, although cooperative effects of histone tail interactions and nucleosome dynamics on chromatin structure will be discussed below.

In addition, molecular simulation models and the biochemical data suggested that electrostatic inter-nucleosomal interactions by histones N-termini can modulate dynamic and flexibility of nucleosome arrays to promote long-distant enhancer-promoter communication between widely separated chromatin locations [33,34,74], likely, through transient folding of nucleosome arrays that facilitates long-range communication.

4. Implications of inter-nucleosomal interactions in chromatin remodeling

The role of multinucleosomal context in chromatin structural

transitions has been emphasized by the formation of ‘altered nucleosome-dimers’ during remodeling of mononucleosomes by the human SWI/SNF complex [75,76]. The SWI/SNF-family remodelers [21–23] possess similar enzymatic activities, such as unwrapping of nucleosomal DNA, nucleosome repositioning and histone octamer transfer [22,77,78]. A particular effect – such as, the octamer transfer [79,80] or sliding [81–85] – may dominate depending on the conditions. In addition, human SWI/SNF [75,76] and related yeast SWI/SNF and RSC complexes [86,87] can join two mononucleosomes to form an ‘altered non-covalent dimer’, in which 50–60 bp of nucleosomal DNA is less protected compared to canonical nucleosomes [75,76,80]. In polynucleosomes human and yeast SWI/SNF can generate structurally altered ‘asymmetric’ pairs of adjacent nucleosomes (‘altosomes’) [86,88]. Altosomes seemingly contain intact histone core octamers, but exhibit an altered MNase digestion pattern [86,88] – protecting one inter-nucleosomal- (220 bp) and one subnucleosomal-sized (70 bp) DNA fragments. Such ‘merged’ nucleosomes are likely formed due to inter-nucleosomal interactions, which promote re-association of the SWI/SNF-unraveled DNA with the surface of neighboring histone octamer that results in a DNA crossover between two adjacent core octamers [79,80,84,87,89–91] (Fig. 1). It is still debatable whether altosomes and ‘altered’ nucleosome-dimers are biologically relevant. However the ‘inverted’ (opposed to canonical nucleosomes) pattern of DNA accessibility [92], and the sub-nucleosomal MNase footprint characteristic for transcribed genes [75,92,93] emphasize the possible role of SWI/SNF-altered nucleosomes in regulating factor access to nucleosomal DNA and generating transcriptionally-active state of chromatin. It is of interest, that yeast ISW1b can also catalyze formation of dimeric structures resembling “altered” dimers (unpublished observation). The DNase/MNase footprint data also suggest that yeast ISW1b- and SWI/SNF-remodeled dinucleosomes possess some common structural features [94].

The remodeling pattern of ISWI-family enzymes [22,23,95,96] can be also affected by inter-nucleosomal interactions. It has been shown that yeast ISW1a can interact simultaneously with two adjacent nucleosomes and exhibited a preference for dinucleosome substrates [97]. Yeast ISW1a, ISW1b and ISW2 differently mobilize histone octamers in mono- vs. dinucleosomes in vitro – such as, ISW1a and ISW2b very similarly repositioned mononucleosomes but produced distinct repositioning patterns for dinucleosomes [98] (Fig. 2). The nuclease footprints of ISW1a/b and ISW2 remodeling products suggest that remodeling of dinucleosomes could result in additional alterations in the nucleosome structure when compared to remodeling of ‘canonical’ mononucleosomes [94,98]. For instance, the extra DNA deprotection in the inter-nucleosomal linker of ISW2-remodeled dinucleosomes, was not observed in unremodeled variably-spaced dinucleosomes (Fig. 3), and, thus, it less likely could be attributed merely to nucleosome sliding. This could rather reflect the remodeling-associated nucleosome alterations which are due to inter-nucleosomal

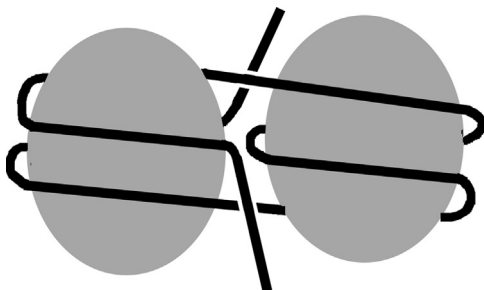


Fig. 1. A schematic illustration of a possible structure suggested for the altosome [88].

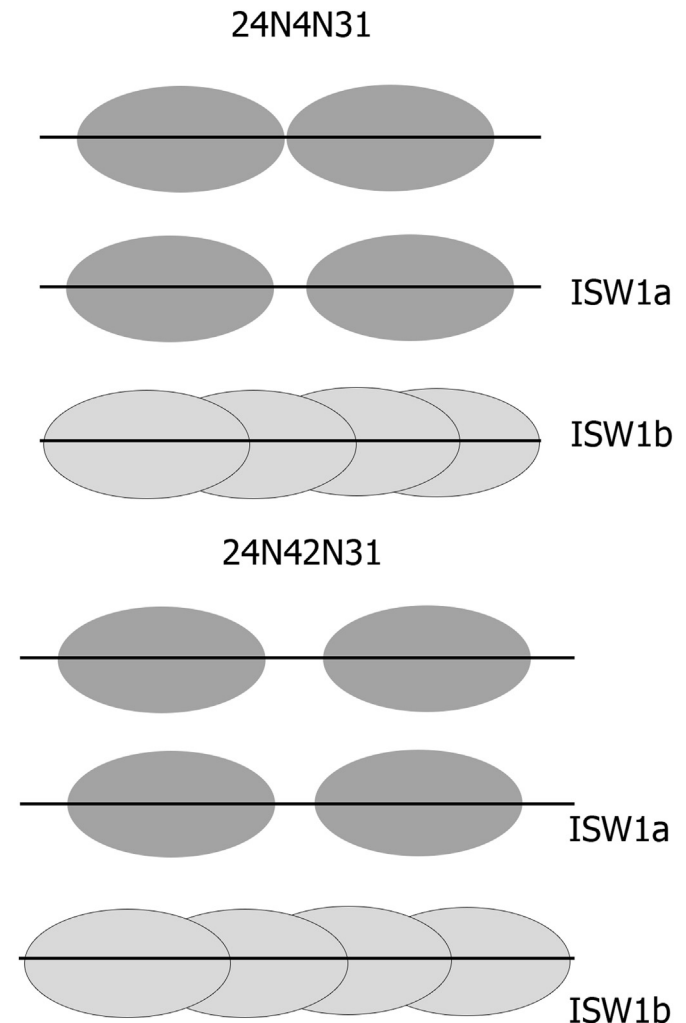


Fig. 2. A schematic illustration of different abilities of ISW1a and ISW1b to remodel dinucleosomes on the example of chromatinized DNA templates 24N4N31 and 24N42N31 (the numbers show the length (bp) of spacer DNA flanking the 601 nucleosome positioning sequences “N”). Positioned nucleosomes are depicted as gray ovals. Depending on the initial nucleosome spacing, ISW1a positions histone octamers closer or further from each other. In contrast, ISW1b randomly distributes histone octamers on the DNA (unpositioned nucleosomes are shown in light gray color).

interactions. Of note, inter-nucleosomal interactions could promote mobilization of nucleosomes by yeast ISW1a and ISW2 even when the extranucleosomal DNA linkers are unfavourably short to support remodelling in mononucleosomes [99]. Thus, alterations in polynucleosomes by remodeling cannot be considered merely as the ‘superposition’ of remodeling effects for the constituent nucleosomes.

5. Inter-nucleosomal interactions and nucleosome structural transitions in nucleosome arrays

Nucleosome array is more correctly to consider as a “sequence of histone core octamers on the DNA” rather than a “sequence of individual ‘canonical’ nucleosomes” due to inter-nucleosomal interactions which affect nucleosome structure. Histone octamers within the chromatin fiber can come together to form ‘compact’ oligomers – such as ‘compact nucleosome dimers’ occupying 260 bp of DNA, ‘compact trimers’ (360 bp), and similar higher compact oligomers [100]. Physicochemical characterization and nuclease footprinting data suggest that these structures represent

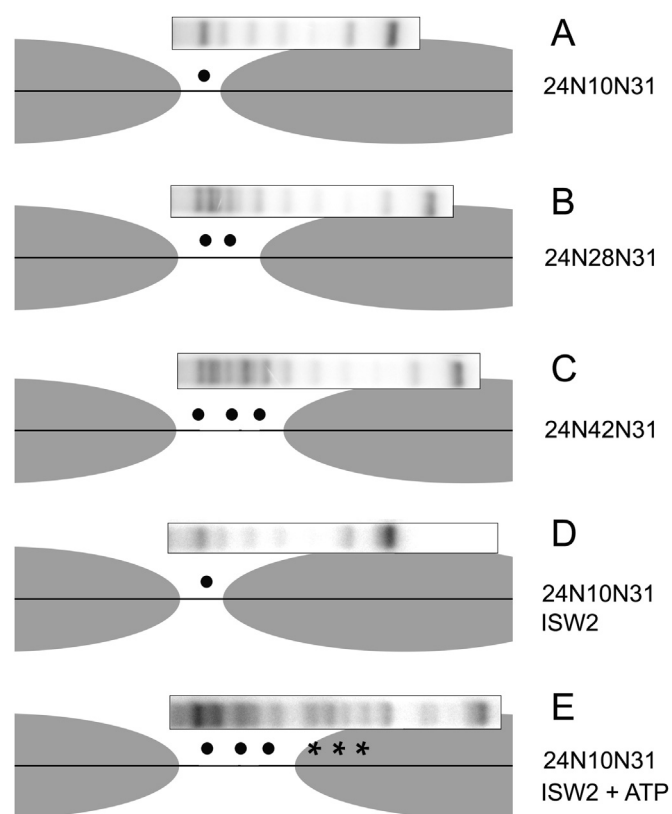


Fig. 3. A sketch illustrating DNase I susceptibility of internucleosomal DNA in dinucleosomes remodeled with ISW2. Nucleosomes were assembled on 3' end-radiolabeled DNA templates 24N10N31, 24N28N31 and 24N42N31 (in which the numbers show the length (bp) of spacer DNA flanking the 601 nucleosome positioning sequences "N"). The gray ovals schematically depict nucleosomes. The insert on each drawing shows a segment of the dinucleosome DNase I footprint ladder (gel direction is from left to right). (A–C) depict unremodeled 24N10N31, 24N28N31 and 24N42N31 dinucleosomes, (D and E) show unremodeled and ISW2-remodeled 24N10N31, respectively. The filled circles indicate the DNase I cleavage sites observed in both unremodeled and remodeled templates, the asterisks indicate extra DNase I sites in remodeled templates. The schemes are shown for illustration purposes and do not maintain exact proportions (for more information see [198]).

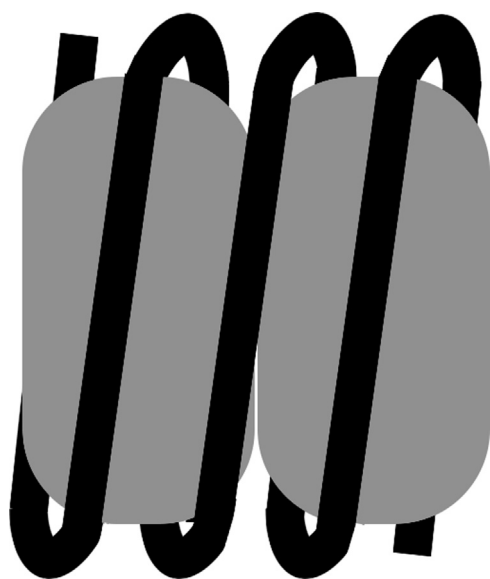


Fig. 4. A sketch of a possible structure suggested for a compact nucleosome dimer [100].

stacked histone octamers with tight DNA wrapping DNA [100] (Fig. 4). Furthermore, interactions between adjacent nucleosomes per se (– i.e. in the absence of remodeling activities) could act to promote DNA unwrapping from histone octamer surface resulting in the eviction of one H2A/H2B dimer and 'dimerization' of two nucleosomes into a single compact particle [101]. In these structures the histone octamer and hexamer 'overlap' by invading each others' space by at least 54 DNA bp with respect to the canonical size of nucleosomal DNA [101]. Transient formation of 'overlapping' nucleosomes could be involved in nucleosomes eviction by yeast SWI/SNF [102] and probably other SWI/SNF complexes in multinucleosomal context [90,103,104]. Spontaneous repositioning of histone core octamers along DNA [105–108] could facilitate nucleosome colliding [101]. In addition, nucleosome overlapping can be promoted by other stimuli facilitating uncoiling of the outer portion of nucleosomal DNA, such as, by binding of transcription factors [109,110] and spontaneous nucleosome unwrapping [111,112].

Besides the ability of the nucleosome to 'merge' with another one, a nucleosome can 'split' in two quasi-symmetric sub-nucleosomal particles consisting of H3/H4 and H2/H2B dimers [113–116], which could possess independent histone modification patterns [114,115]. The existence of "half-nucleosomes" in transcribing genes was discussed over decades [117,118] (reviewed in [119]), although the mechanisms underlying their formation and details of their structure still remain debatable.

6. Inter-nucleosomal interactions and intrinsic nucleosome dynamics in nucleosome arrays

Spontaneous (10–250 ms) unwrapping of nucleosomal DNA [111,112,120,121] was predicted decades ago [122,123]. These transient nucleosome alterations include short-range 'breathing' and a longer-range 'opening' [119,120,124] (which is particularly efficient at the outer nucleosome regions [125,126]). Nucleosome spontaneous fluctuations are considered as one of the major factors that regulate access of transcription factors to nucleosomal DNA [19,109,111,112]. Furthermore, fluctuations of DNA coiling around histone octamer promote the polymerase to overcome the nucleosomal barrier [127–131], so that RNA polymerase functions as a Brownian ratchet relying on a transient exposure of the DNA. Under physiological conditions can be also observed other types of nucleosome fluctuations—such as, for example, nucleosome 'gaping' [132–135] – a slow (1–10 min) spontaneous hinge-like nucleosome opening in the direction normal to DNA plane (Fig. 5).

It has been shown, that binding of massive ligands (transcription factors) to DNA near the edge of the nucleosome promotes transient unwrapping of DNA, likely, due to steric and/or electrostatic effects [109,110]. In this way transcription factors could facilitates each others' access to buried DNA sequences by increasing the time DNA remain exposed. Single-pair FRET experiments using dinucleosomes showed that interactions between two adjacent histone octamers drastically shift the dynamic equilibrium between wrapped-unwrapped DNA states that promotes uncoiling of the outer portions of nucleosomal DNA [136]. The effect is likely based on the electrostatic repulsion. However, the 'pulling' force applied to nucleosomal DNA by the stochastic motion of the adjacent nucleosome could also play a role. The effect from neighboring nucleosome depended on the length of inter-nucleosomal linker as well as on the nucleosome phasing (relative to the DNA pitch), and varied on the proximal and distal sides of the test (– i.e. dye-labeled) nucleosome [136]. This emphasizes an essential role of inter-nucleosomal interactions in the modulation of inherent nucleosome dynamics and accessibility of nucleosomal DNA. Of note, long extranucleosomal DNA linkers could also facilitate

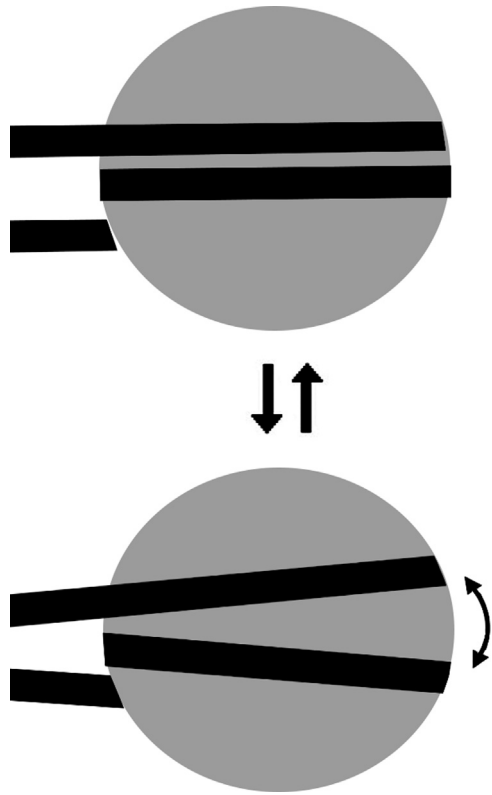


Fig. 5. A schematic illustration of nucleosome gaping transition – an about 30° ‘opening’ of the nucleosome in the direction normal to the DNA plane. The complex alterations of the histone core octamer (which include distortions of the histone dimer-tetramer interactions) are not depicted.

transient uncoiling of mononucleosomes, likely, by electrostatic repulsion of DNA linkers at the nucleosome entry-exit [136]. Studies using restriction endonucleases (RE) to monitor nucleosome fluctuations also demonstrated significantly increased exposure of nucleosomal DNA in dinucleosomes when compared to mononucleosomes [137]. The spFRET studies of Mg^{++} -dependent folding of tri-nucleosome arrays [138], demonstrated both rapid conformational dynamics and high rate of spontaneous DNA exposure even when nucleosome arrays were in compact states [138]. Of note, structural fluctuations of the nucleosome can be affected by histone modifications. Chemical acetylation of core histones noticeably increases the rate of nucleosome opening [139]. Specific acetylation of nucleosomes at histone H3 K56 results in 7-fold increased breathing of the outer 30 bp stretches of nucleosomal DNA [140,141].

A combination of spFRET with optical tweezers (that allow to evaluate the directionality of nucleosome unwrapping), revealed that under applied force the spontaneous opening of outer DNA coils is directional and asymmetric [142]. The data suggest that (i) nucleosomes preferentially unwrap from the end containing DNA sequences which are more ‘mechanically’ stiff (and which less tolerate bending around a histone octamer [143–145]), and (ii) transient unwrapping of DNA on one end of the nucleosome stabilizes DNA coils on the other end even if DNA on both sides of the nucleosome has similar stiffness [142]. This is consistent with earlier predictions that unwrapping of the nucleosome on one end eliminates the electrostatic repulsion between the two DNA gyres and so stabilizes the DNA on the other end [146,147]. Of note, the unfolding asymmetry significantly enhances the directionality of nucleosome unfolding, so that small differences in the DNA stiffness could result in strong unwrapping preference of one nucleosome end over the other [142]. Although the earlier ALEX-

spFRET studies reported evidence for spontaneous DNA unwrapping from both ends of free, diffusing nucleosomes [126], however it remained unresolved if in these studies nucleosome unwrapping on one end was not accompanied by rewinding of the other end. In addition, in spFRET/optical tweezers experiments nucleosomes are stretched at a finite rate providing an insight on the relative barriers of DNA unwrapping compared to a larger time-scale spontaneous unwrapping [142].

It seems likely, that the ‘under-force’ conditions adequately recapitulate behavior of nucleosome particles *in vivo*, which are flanked on both sides with extended nucleosome arrays anchored to nuclear structures. In general, DNA torsional tensions, an important regulator of chromatin structure, are generated *in vivo* in virtually any process that changes the supercoiling of the chromatin loop domains or manipulates DNA strands forcing the DNA to revolve around its axis [148,149]. For instance, DNA tensions generated by the movement of the RNA polymerases (as directly observed *in vivo* [150–153] and *in vitro* [154,155]) are thought to play a role in unfolding–refolding of nucleosomes before- and after the waking RNA polymerase, respectively [131,149,156,157].

7. Molecular bases for the implication of inter-nucleosomal interactions in biological processes

Thus, the intrinsic structural features and dynamics of nucleosomes can play important role in the determination of chromatin structural/functional states. Internucleosome interaction can facilitate nucleosome spontaneous unwrapping and promote formation of a highly-dynamic, accessible state of nucleosome arrays. The asymmetry of nucleosome transient unwrapping could further contribute to chromatin dynamics and orchestrate the occurrence of DNA-based processes. By preventing unzipping of DNA beyond the nucleosome dyad (that causes dissociation of the histone octamer [145]) unfolding asymmetry could stabilize nucleosomes upon the transient release of one H2A/H2B dimer during transcription [130,131,158,159], ATP-dependent remodeling [21,96,103,160], or H2A/H2B dimer exchange (such as, the sequential H2A/H2A.Z cycling by SWR-C/SWR-1 [161,162]). The ability of adjacent nucleosomes to accommodate temporary detached histone octamers [35–40] or dimers/tetramers [40,44] could further diminish the histone eviction. Thus, (i) by facilitating nucleosome unwrapping, (ii) by coordinating ‘sequential’ unwrapping of both ‘halves’ of the nucleosome, and (iii) by providing temporary docking interface for histone octamers, these mechanisms could ensure full accessibility of nucleosomal DNA without histone octamer eviction. In addition, the inherent strong directionality of nucleosome unwrapping could assist ‘directional’ chromatin-based processes – such as, it can ensure correct transcription initiation and repress cryptic antisense transcription [163,164]. The inter-nucleosomal interactions could further enhance the transcription ‘polarity’ observed with transcribing mononucleosomes *in vitro* [165].

For example, the effects of inter-nucleosomal interactions and orchestrated dynamics of nucleosome unwrapping could play a role in the mechanisms underlying the *in vivo* transcription of nucleosome arrays occurring without significant loss of histone octamers at speeds comparable to transcription of naked DNA templates *in vitro* [166–168] – whereas, in contrast, a single nucleosome is sufficient to present a strong barrier to transcription elongation *in vitro* [131,159,169]. It is of note, that +1 nucleosome (the first nucleosome downstream the transcription start site), when not displaced by loading polymerase, presents *in vivo* a much greater transcription barrier than nucleosomes at downstream positions [169–172]. According to the scenario we propose (Fig. 6), transient uncoiling of the promoter-proximal boundary of

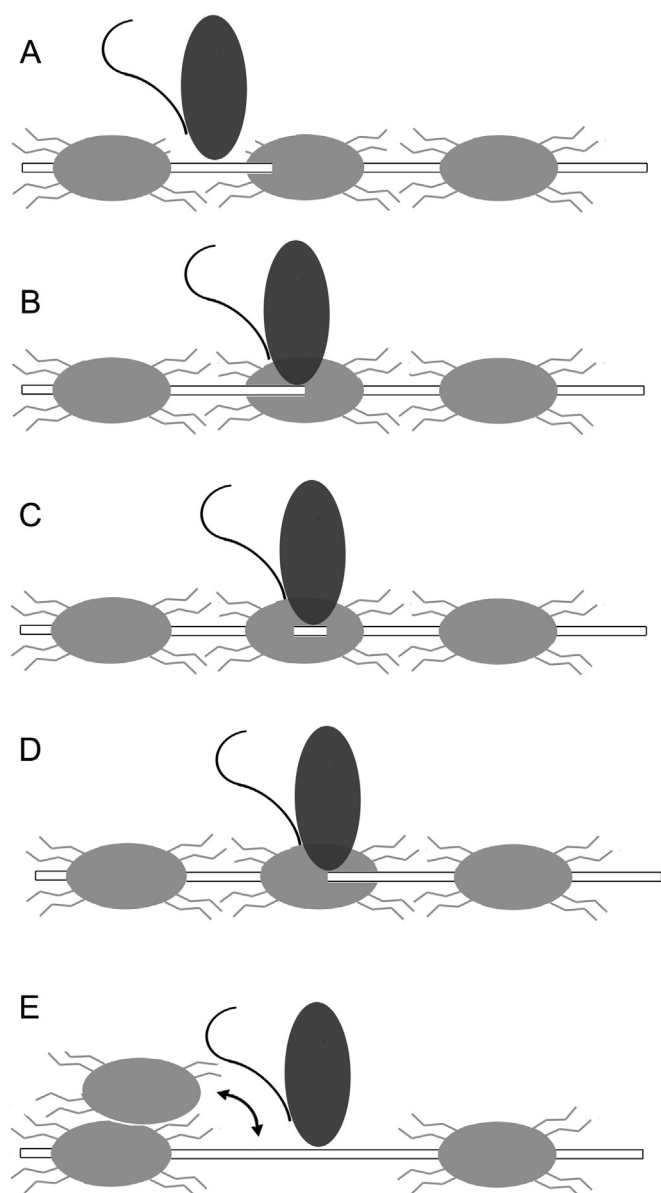


Fig. 6. Possible role of internucleosomal interactions and inherent nucleosome dynamics in RNA polymerase II transcription through arrayed nucleosomes. (A) Internucleosomal interactions facilitate transient uncoiling of DNA that allows RNA- pol II to enter the nucleosome. (B) RNA Pol II enters the nucleosomes and pauses at the region of strong histone-DNA interactions. (C) recoiling of the DNA behind the polymerase promotes formation of temporary DNA ϕ -loop, that is required to position RNA pol II on the DNA, and also (D) orchestrates uncoiling the promoter-distal portion of the nucleosome that allows RNA pol II to “read” through the rest of the nucleosome. (E) Neighboring nucleosomes could transiently accommodate the ‘transcribed’ histone octamer (or its’ dissociated components) and thus, promote further reinstatement of its position on the DNA.

the nucleosome, facilitated by inter-nucleosomal interactions, allows RNA-polymerase II to enter the nucleosome. As the RNA Pol II proceeds towards the dyad and pauses at the region of strong histone-DNA interactions [128,129,131,173], recoiling of the DNA behind the RNA Pol II promotes formation of temporary intra-nucleosomal DNA loop (ϕ -loop, zero-loop) that is critical for proper positioning of the RNA Pol II active center on the DNA [131,159]. At the same time, the re-association of the DNA with histone octamer behind the enzyme with ϕ -loop formation energetically favors unwrapping of the DNA ahead of the polymerase that allows transcription of the rest of the nucleosome [173–176]. Or, reciprocally, transient unwrapping of the nucleosome end in

front of the polymerase could orchestrate nucleosome re-wrapping (with ϕ -loop formation) behind the polymerase. Thus, transcription through the nucleosome could be accompanied by transient detachment of only one H2A/H2B dimer without complete nucleosome eviction [131]. In this scenario, intrinsic nucleosome dynamics could act in cooperation with transcription cofactors (– e.g. FACT, which coordinates removal/re-association of H2A/H2B dimers [177–181]) to promote orchestrated unwrapping/rewrapping of the nucleosome. In addition, due to the propensity to accept an extra histone octamer or H2A/H2B dimers [35–40,40,44], neighboring nucleosomes could promote stabilization of the ‘transcribed’ histone octamer (or transiently accommodate its’ dissociated components), and so contribute to the reinstatement of nucleosome positioning in the wake of RNA Pol II. This could be particularly important at high transcription rates, which, for instance, cause complete displacement of histone octamers in mononucleosomes *in vitro* [173,182–184].

The inherent dynamics of nucleosomes in multinucleosomal environment might be implicated in many other chromatin-based processes – such as, in promoting chromatin access to histone modifying complexes (see Section 2) or in modulating the pattern and outcome of chromatin remodeling (see Section 3). Inter-nucleosomal interactions could stabilize transient structural alterations in chromatin caused by ATP-utilizing remodeling enzymes. Together with nucleosome inherent dynamics this could promote formation of steady-state chromatin structures with increased dynamics and accessibility. Histone post-translational modifications could modulate histone tail interactions and nucleosome dynamics, and thus, could ‘program’ some ‘structural code’ of chromatin activity states.

In this respect are of interest studies, which have shown that transcriptionally-active minichromosomes in yeast [185,186] and mammalian cells [187] exhibit high degree of DNA ‘thermal untwisting’ (– i.e. the ability of DNA in solution to change its twist in response to temperature shift [188,189]). DNA thermal untwisting is severely repressed in chromatin assembled from histones and DNA *in vitro* [190–193]. In other words, DNA of studied transcriptionally-active minichromosomes [185–187] exhibited some dynamic features of bare DNA despite being assembled in nucleosomes. It could be speculated that high degree of DNA thermal flexibility represents a feature of transcriptionally-active chromatin *in vivo* [190,194]. Of note, high degree of ‘thermal untwisting’ of minichromosomal DNA was preserved in isolated nuclei [187] or in isolated minichromosomes [185], but was not observed in mononucleosomes of transcriptionally-active genes [190] (isolated via Hg-affinity chromatography [195–197]). This allows excluding the possibilities that high thermal flexibility of studied minichromosomes was solely due to the specific modifications of active chromatin or ongoing ATP-dependent chromatin remodeling. It would be attractive to speculate that high conformational flexibility of ‘active’ minichromosomes has a direct link with the nucleosome interactions and dynamics discussed in this manuscript. However, the structural bases and underlying mechanisms of this phenomenon still remain to be clarified.

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Appendix A. Transparency document

Transparency document associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bbrep.2016.02.009>.

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