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

Wladyslaw A. Krajewski

Institute of Developmental Biology of Russian Academy of Sciences, ul. Vavilova 26, Moscow, 119334 Russia

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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.

Contents

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

E-mail address: wkrajewski@hotmail.com

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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 co-operatively 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 $MgCl_2$ (unpublished observation). Interestingly, gel-purified mononucleosome-dimers tend to dissociate into individual mononucleosomes upon freezing-thawing at a $-80\,^{\circ}C$ (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 $\sim$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