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Minireview

Chromatin organization in relation to the nuclear periphery

Bernike Kalverda, Michael D. Röling, Maarten Fornerod*

Department of Tumor Biology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

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Abstract In the limited space of the nucleus, chromatin is organized in a dynamic and non-random manner. Three ways of chromatin organization are compaction, formation of loops and localization within the nucleus. To study chromatin localization it is most convenient to use the nuclear envelope as a fixed viewpoint. Peripheral chromatin has both been described as silent chromatin, interacting with the nuclear lamina, and active chromatin, interacting with nuclear pore proteins. Current data indicate that the nuclear envelope is a reader as well as a writer of chromatin state, and that its influence is not limited to the nuclear periphery.
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1. Chromatin organization by compaction

To fit into the limited space of the nucleus and still carry out its function, human genomic DNA is extensively folded, making it about 10000-fold more compact. Several levels of compaction have been described: the nucleosome, the 30 nm fiber and higher order chromatin structure.

The lowest level of chromatin compaction is the nucleosome. A 5–10-fold compaction is achieved when 146–165 base pairs of DNA are wound around an octamer of histone proteins, which is referred to as the nucleosome core particle. Besides providing a structural basis for the first compaction level, histones can also affect chromatin organization by being chemically modified at their tail or by being replaced by variants of the core histones. These modifications have a major impact on chromatin structure and gene expression by influencing the binding of proteins to the nucleosome, the affinity of DNA for the histone octamer and the stability of higher order structures [1]. Thus, at this low level of organization the nucleosome offers a powerful mechanism for controlling chromatin structure in a local, non-random manner.

Findings on the second level of compaction are more ambiguous. In vitro, oligonucleosomes are able to organize themselves into a compact fiber with a diameter of 30 nm in absence of nuclear proteins but in the presence of divalent cations. In vivo, estimated nuclear cation concentrations are even higher than the concentration used in experiments, aiding the compaction [2]. This compaction could be further modulated by the involvement of numerous nuclear proteins in vivo. For example, histone tails and histone H1 further stabilize this structure by binding to linker DNA.

All condensation levels above the 30 nm fiber are indicated as higher order chromatin structure. This poorly defined structure may consist of several levels of condensation and is very dynamic and thus hard to study. The question has even been raised whether there is a uniform higher order structure at all, or whether chromatin is too dynamic to form stable structures at a higher order level [3].

All levels of compaction are not equal throughout the cell, leading to more accessible and less accessible regions. Dynamic chromatin-binding proteins and histone modifications play key roles in dynamically compacting the chromatin or opening it up, giving the cell the possibility to rapidly alter chromatin compaction at multiple regions when necessary. Chromatin compaction can control processes like transcription, duplication and repair by limiting the accessibility of chromatin by proteins. Knowing this, it is not surprising that disturbance of chromatin structure has been linked to several types of disease, including cancer [4].

2. Chromatin organization by insulator activity

To prevent spreading of condensed, silent chromatin to more open and active regions, insulators can form a barrier between these distinct chromatin domains. Insulators have been defined as genomic elements and their interacting proteins can block distal enhancer activity or protect chromatin against effects from a neighboring chromatin region when positioned adjacent to it [5]. The first insulator discovered was the *gypsy* transposable element, which blocked enhancers from activating the yellow gene when inserted upstream of the *yellow* gene promoter [6]. A complex of proteins binding to the *gypsy* insulator has been identified, consisting of Su(Hw), Mod(mdg4), CP190 and dTopors [7–9]. In yeast, insulators have been found to form boundaries that block spreading of silenced chromatin at telomeres and from the mating-type loci HML and HMR. In vertebrates, examples of insulators are those in the chicken β-globin genes and the human T cell receptor-α/δ locus [5]. The boundary function of some insulators has been shown to be dynamic, as the insulator function can be modified or abrogated by modifying factors and DNA methylation [5]. Although still several models exist for the mechanism of insulator function, much data points in the direction of a loop-domain model. For instance, inserting two copies of the Su(Hw) insulator

*Corresponding author. Fax: +31 20 5122029.
E-mail address: m.fornerod@nki.nl (M. Fornerod).

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element instead of one copy inhibited the insulator function, suggesting that the insulator activity can be overcome by a loop formed by the insulator elements interacting together [10,11]. When an enhancer was flanked by two Su(Hw) insulator sites, blocking of activity was more severe, suggesting that by forming a loop around the enhancer, enhancer–promoter interactions are being blocked [10]. Thus, insulators are suggested to establish a higher order chromatin structure by the formation of loops or possibly more complicated structures.

3. Chromatin organization at the nuclear periphery

Are differently compacted or structured chromatin regions distributed in a random way inside the nucleus, or do some regions prefer certain sites? To address this question, a fixed nuclear viewpoint is required. For this reason extensive research has been performed into localization of chromatin in relation to the nuclear envelope and the putative role of the nuclear envelope in chromatin organization. The first hint that differently compacted and structured chromatin regions are distributed non-equally in the nucleus dates from about a century ago. Classical cytological characterization of the nucleus discerned two types of chromatin: the relatively dark staining heterochromatin that stays condensed throughout interphase and lighter staining euchromatin (''real'' chromatin) which decondenses in interphase and is traditionally associated with transcriptional activity [12]. Interestingly, in many cell types, classically defined heterochromatin has a different subnuclear distribution than euchromatin, with heterochromatin enriched at the nuclear periphery and around nucleoli [13]. It has been suggested for a long time that this non-random distribution of heterochromatin and euchromatin has a function and that attachment of chromatin to the nuclear envelope is important to obtain the three dimensional organization of the chromatin fibers [14,15]. These suggestions are based both on the rationale that the nuclear envelope is the only stable structure in the nucleus at which chromatin can be organized structurally and on experimental data showing that chromatin fibers are attached to the nuclear envelope [16,17]. In 1968, Comings concluded on the basis of electron microscopic images of labelled nuclei that there is a certain degree of order in interphase chromatin and suggested that the order might be maintained by attachment of chromatin to the nuclear envelope. Blobel extended this view by suggesting a 'gene-gating' hypothesis: compact chromatin associates with the nuclear lamina, while expanded transcribable genes associate with the nuclear pore complex, aiding in nuclear export of RNA. He proposed that the non-random distribution of nuclear pore complexes in the nuclear envelope reflects the non-random organization of chromatin. However, whereas the models of Comings and Blobel were logically and intuitively sound, at their time not many data were present to confirm their ideas. Now the situation is different, as many new techniques in both microscopy and the use of microarrays have boosted research in the chromatin field.

4. Chromatin at the nuclear periphery: from stainings to genes

The first genetic elements that were found to be localized to the nuclear periphery were telomeres, the ends of chromosomes. Already in 1885, observations about the positioning of chromatin in cells were made by Carl Rabl, who observed in salamander nuclei that centromeres clustered at one pole and telomeres at the opposite pole [18]. Peripheral telomeres have also been observed in *Drosophila* [19,20], Trypanosoma, plant cells, vegetatively growing fission yeast, but not in mammalian cells [21,22].

The first studies that systematically mapped genomic loci in relation to the nuclear periphery were performed in *Drosophila* polytene-chromosome containing cells. It was found that specific chromosomal loci associated with the nuclear envelope with a high frequency [19,23–25]. Interestingly, those loci often corresponded to ''intercalary heterochromatin'', linking the concept of inactivity of peripheral heterochromatin to genomic maps. Two decades later, high resolution molecular mapping in *Drosophila* cells confirmed this link and revealed that genes that associate with the nuclear lamina are transcriptionally silent (further described below) [26]. In human cells, the first study that went beyond localization of bulk staining was the localization of the inactive X chromosome at the nuclear periphery [27]. Chromosome-specific fluorescent in situ hybridization revealed that autosomes too have their preferred position [28], correlating with gene density: gene-poor chromosomes tend to localize to the nuclear periphery (e.g. human chromosome 18), while gene-rich chromosomes tend to localize at intranuclear positions [29].

5. Silencing at the nuclear periphery: cause or consequence?

Does localization at the periphery cause chromatin silencing or is the peripheral localization a consequence of inactivation? In yeast, presence at the nuclear periphery has been correlated with inactivity of genes by a study in which a RNA polII transcribed gene was inserted adjacent to telomere sequence and thereby was repressed, a process called telomere position effect (TPE) [30]. Yeast telomeres cluster at the nuclear periphery as do proteins that are essential for TPE. However, it was shown that localization to the nuclear periphery is not necessary nor sufficient for TPE [31] and there is no correlation between TPE levels and extent of localization [32].

Telomere-independent silencing of genes at the nuclear periphery was tested in yeast by tethering genes artificially to the nuclear envelope by fusing integral membrane proteins to the Gal4 DNA-binding domain [33]. Several of these membrane proteins caused silencing. The mechanism by which the silencing occurs has been suggested to be the higher concentration of SIR proteins at the periphery, as overexpression of SIR3 and SIR4 improved silencing in strains with defective silencers. Telomere clusters colocalize with Sir3p, Sir4p and Rap1 [34]. Seventy percent of these foci is at the nuclear periphery and does not directly associate with nuclear pore complexes, nor does provocation of nuclear pore clustering at one side of the nucleus affect the position of the telomere foci. In this study, resolution was too low to determine whether subnuclear position was altered in absence of Sir3p or Sir4p. Recently, it has been found that the Sad1-UNC-84 (SUN) domain protein Mps3 is required for anchoring of telomeres to the nuclear periphery by binding Sir4 [35].

Observations in higher eukaryotes also indicate a repressive role of the nuclear envelope. IgH loci move away from the nu-

clear envelope in B cells before their activation [36]. Also, when CFTR and adjacent genes are transcriptionally inactive, they are preferentially associated with the nuclear periphery, while in their actively transcribed states this locus associates with euchromatin in the nuclear interior [37].

6. Silent chromatin at the nuclear lamina: towards a mechanism

In metazoans, the inner surface of the nuclear envelope is lined with a filamentous protein network termed the nuclear lamina. This network consists primarily of lamins, which are members of the intermediate filament protein family. Lamins can be anchored to the inner nuclear membrane via isoprenylation of a CaaX motif, or through interactions with integral membrane proteins. Two major types of lamins can be distinguished. A-type lamins are expressed in a developmentally controlled manner, while B-type lamins are ubiquitously expressed and essential for cell viability. Interestingly, mutations in A-type lamins and the lamina-associated protein emerin have been linked to a variety of hereditary diseases [38–41]. There are several indications that the nuclear lamina directly interacts with chromatin (reviewed in [40,42]). Lamins bind in vitro to core histones [43] and to specific DNA sequences termed Matrix Attachment Regions [44]. The tail domain of *Drosophila* lamin B binds in vitro to polynucleosomes, which can be competed by histone H2A or H2B [47]. The lamin B receptor, a nuclear membrane protein that interacts with lamin B, has been reported to bind in vitro to DNA, histone H3–H4 tetramers, mitotic chromosomes and the heterochromatin protein HP1 [43,45–48]. Finally, by electron microscopy it has been shown that some chromatin is in close contact with the nuclear lamina [49,50]. Based on these observations, the nuclear lamina has been hypothesised to have key roles in both chromatin organization and gene regulation [41,51–55]. Using a genome-wide in vivo approach, about 500 genes were identified in *Drosophila* that preferentially interact with B-type lamin [26]. These genes are transcriptionally silent, lack active histone marks, replicate late and are widely spaced. Using a proteomics approach, also in vertebrate cells a lack of active histone marks was detected in nuclear lamina-associated chromatin [56]. Interestingly, the histone deacytylase HDAC3 interacts with the lamin-associated protein LAP2β [57], suggesting that the nuclear lamina can play an active role in gene silencing. However, in vivo it remains an area of intensive research to find out what mechanistically tethers chromatin to the nuclear lamina.

7. Active genes at the nuclear periphery: roles for nucleoporins?

In contrast to findings of localization of inactive chromatin at the nuclear periphery, it has also been found that some dynamically regulated genes are recruited to the nuclear periphery when activated [58–60]. Also, artificial tethering of genes to the nuclear envelope in yeast has been reported multiple times to enhance transcription [60–62]. It seems that this is not a yeast-specific phenomenon. Early work by [63] in vertebrate cells indicated that DnaseI sensitive chromatin preferably localizes at the nuclear periphery. More recently, Ragoczy et al. [64] showed that at the time of activation, the β-globin locus is localized at the nuclear periphery and only moves into the nuclear interior at a later time point.

The main non-lamina structures at the nuclear periphery are the nuclear pore complexes (NPCs) that permeate the double nuclear membrane and are composed of approximately 30 different proteins termed nucleoporins or nups (reviewed in [65]). In yeast, active genes have been found to interact with nucleoporins [58]. The same genes also interact with the transcriptional regulator Rap1 and with nuclear transport receptors (Kap95, Cse1, XpoI/CRM1) [58]. Together with the observation that nucleoporins at the nucleoplasmic side of the nuclear pore complex are moving dynamically between the nuclear pore complex and the nucleoplasm [66–69], this indicates that it remains possible that chromatin/nup interactions so far detected partly or completely take place in the nuclear interior. Interestingly, the dynamic moving of Nup98 and Nup153 between the nuclear pore complex and the nucleoplasm and/or cytoplasm is dependent on transcription [69,70].

In another study in yeast, a micrococcal nuclease was fused to Nup2 and the construct was shown to be at the nuclear periphery in 80% of the cases. It was shown that at single loci and throughout chromosome 6 cleavage by the nuclease mainly took place at promotors [71]. However, in this study no relation with gene activity was made. At specific loci, the role of proteins of the nuclear pore and the transport machinery has been studied, leading to different conclusions. Several studies have shown that Nup2 interacts with the active *GAL1* locus [58,59,71,72]. However, Brickner et al. found that Nup2 is essential for *GAL1* (and *INO1*) recruitment to the periphery [62], whereas Cabal et al. conclude that neither Nup2 nor Nup60, which tethers Nup2 to the pore [73], is essential [74]. They also found that Mlp1 is not essential for *GAL10* and *HDP104* recruitment, whereas Dieppois et al. reported the opposite [75].

In *Drosophila* it has been shown that the nucleoporins Mtor/TPR and Nup153 are required for dosage compensation by X-chromosome activation in males and that the activated X is localized at the periphery [76], suggesting a mechanistic role of tethering chromosomes to the nuclear pore complex in gene activation. Using Chip-on-Chip analysis, Casolari et al. studied which genes associate with the nucleoporin Mlp1 before and after the mating transcriptional program was switched on by pheromones [59]. They showed different genes associated with Mlp1 after induction of the mating transcriptional program. However, no correlation was found between transcriptional activity and Mlp1 association, making the question of why genes start to interact with the nuclear pore complex the more insisting. Also recent chip-on-chip analysis of nucleoporin Nup93 in vertebrate cells did not reveal association with transcriptional activity [77]. In yeast, loss of Sac3 or Mex67 blocks recruitment of the *GAL1-10* locus to the periphery [74,75], suggesting that besides the nuclear pore components themselves, also the mRNA transport machinery has a role in recruitment or maintenance [78] of active genes to the nuclear periphery. However, the distinction between mRNA export factors and nucleoporins may not be as evident as it seems, as mRNA export factors are enriched at the nuclear pore complex, many nucleoporins are shuttling between the nuclear pore complex and the nucleoplasm and nucleoporins have been suggested to have functions in mRNA transcription [79]. It is therefore uncertain whether the similar observations for nucleoporins and mRNA export factors concerning their interaction with genomic loci and influence on their localization point to a similar role in mRNA export or in chromatin organization at the nuclear pore complex.

Apart from activating gene expression, nucleoporins in yeast also have been suggested to acts as genomic insulators, blocking the action of enhancer elements. Physical tethering of genomic loci to Nup2p blocks the spreading of heterochromatin [72] but other components of the nuclear pore complex do not do this. As Nup2p is a dynamic component of the nuclear pore complex, it cannot be ruled out that the insulator function of Nup2p is not taking place at the nuclear pore but instead in the nucleoplasm. Interestingly, in *Drosophila* a link has been found between lamin and dTopors, a component of the Su(Hw) insulator complex [9]. dTopors colocalizes with lamin and mutations in lamin disrupt dTopors localization at the nuclear periphery. Consistent with these data is the possibility that insulators are present at the nuclear periphery between inactive, nuclear lamina-bound genomic regions and active nuclear pore-bound loci (Fig. 1).

8. The nuclear periphery: both reader and writer of chromatin organization?

The nuclear periphery is unique because it contains the only stable structures that contact the chromatin: the nuclear lamina and nuclear pore complexes. As we have discussed above, the extend to which the nuclear pore complexes still can be viewed in this way is uncertain. Nevertheless, the stability of the nuclear lamina remains unchallenged, and high resolution interaction mapping of chromatin/lamin interaction may give a "footprint" of interphase chromatin structure. Importantly, association of a reporter gene to a nuclear lamina localized tether resulted in epigenetic silencing of the reporter as well as adjacent endogenous genes [80], indicating that the nuclear lamina also acts as a writer of chromatin organization. However, only some, not all, genes are silenced upon nuclear periphery recruitment [81]. Chromatin in the nucleus has been shown to undergo rapid constrained Brownian motion [82,83] and can move over several microns on a longer time scale [84,85]. Thus, genes may move back and forth between the nuclear periphery and interior in each individual nucleus over time (Fig. 1). In addition, positioning of chromosomes inside the interphase nucleus may be determined during the previous mitosis, and is likely to be subject to a certain degree of randomness [86]. As a consequence, different chromosomal regions may have a specific probability to be influenced by the nuclear periphery, both at the individual and population level. Given this dynamic and stochastic nature of chromatin posi-

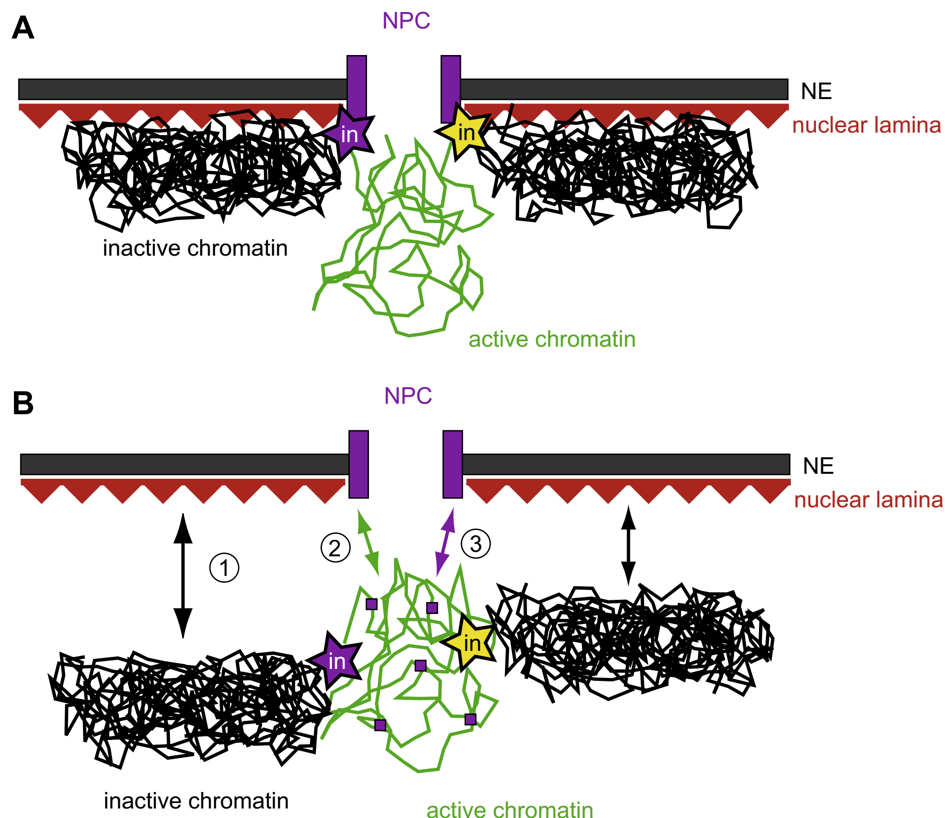

Fig. 1. Chromatin organization in relation to the nuclear periphery: a static (A) and dynamic (B) view. (A) Repressed chromatin associates with the nuclear lamina via an as yet unknown mechanism, possibly involving multiple types of contact. At the periphery histone deacetylation may contribute to the silenced state. Components of the nuclear pore complex (NPC) interact with active chromatin, and nuclear pore complexes (NPC) components such as Nup2 (purple stars) or nuclear factors like dTopors or Su(Hw) (yellow stars) may act as insulators (in) between active and repressed chromatin at the nuclear periphery. (B) Repressed chromatin dynamically interacts with the nuclear lamina, possibly attracted by higher order structure or by specific nucleosome state. Active chromatin similarly interacts dynamically with the NPC (2). Also, NPC components (purple) may shuttle into the nucleoplasm (3). In these ways, the nuclear envelope may exert its function beyond the nuclear periphery. Insulators are found in the nucleoplasm as well as at the nuclear periphery.

tion, the nuclear lamina may be reader and (co-)author of the organization of the entire genome, and not just of the chromatin at the nuclear periphery.

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