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REVIEWS

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Compartmentalization of the Cell Nucleus and Spatial Organization of the Genome

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Abstract—The eukaryotic cell nucleus is one of the most complex cell organelles. Despite the absence of membranes, the nuclear space is divided into numerous compartments where different processes involved in genome activity take place. The most important nuclear compartments include nucleoli, nuclear speckles, PML bodies, Cajal bodies, histone locus bodies, Polycomb bodies, insulator bodies, and transcription and replication factories. A structural basis for the nuclear compartmentalization is provided by genomic DNA, which occupies most of the nuclear volume. In turn, nuclear compartments guide the chromosome folding by providing a platform for spatial interactions of individual genomic loci. The review discusses the fundamental principles of higher-order genome organization with a focus on chromosome territories and chromosome domains and considers the structure and function of key nuclear compartments. It is shown that the functional compartmentalization of the cell nucleus is tightly interconnected with genome spatial organization, is highly dynamic, and is based on stochastic processes.

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INTRODUCTION

A nuclear compartment can be defined as a site where a certain set of macromolecules concentrates in the cell nucleus. Nuclear compartments are often equated with the so-called nuclear bodies, which are function-dependent aggregations of macromolecules involved in a particular process occurring in the cell nucleus [1–4]. The nucleolus is the most recognizable compartment of the kind (Fig. 1a). Other compartments include, but are not limited to, a perinucleolar compartment, Cajal bodies, PML (ND10) bodes, histone locus bodies, speckles, and transcription and replication factories (Fig. 1). The majority of the compartments were initially identified by light or electron microscopy. For instance, splicing bodies, which are detectable by staining small nuclear RNAs (snRNAs) and spliceosome assembly proteins (e.g., SC35), were first described as granules seen in the interchromatin space under an electron microscope. Cajal bodies were similarly observed in vertebrate neurons by light microscopy. As immunostaining developed and nuclear body proteins were identified, it became possible to rapidly visualize the nuclear bodies and to examine them subsequently by confocal microscopy.

Nuclear bodies were for a long time studied without regard to the spatial organization of interphase chromosomes. Yet genomic DNA was always known to play a role in biogenesis of many nuclear compartments. For instance, nucleoli form around transcribed rRNA genes. Many nuclear compartments arise around certain genomic loci, as is the case with histone locus bodies or transcription and replication factories. Even if not involved directly in assembly of nuclear compartments (e.g., in the case of speckles, paraspeckles, PML bodies, and some other compartments), genomic DNA still plays a substantial role in their positioning because the nuclear space is occupied by chromatin, while the above compartments occur in chromatin-free regions. Thus, the genome packaged in the nuclear space can be thought to provide a basis for nuclear compartmentalization, which, in turn, is directly related to genome activity [5–8]. In addition, it should be mentioned that certain chromatin structures are often classified with nuclear compartments, as is the case with pericentric heterochromatin clusters (chromocenters), perilamellar (peripheral) and perinucleolar layers (Fig. 1b) [9], Polycomb bodies, and some other compartments. Finally, the space occupied

Abbreviations: snoRNA, small nucleolar RNA; snRNA, small nuclear RNA; RNP, ribonucleoprotein; FISH, fluorescence in situ hybridization, HiC, high-throughput chromosome conformation capture; SINE, short interspersed element.

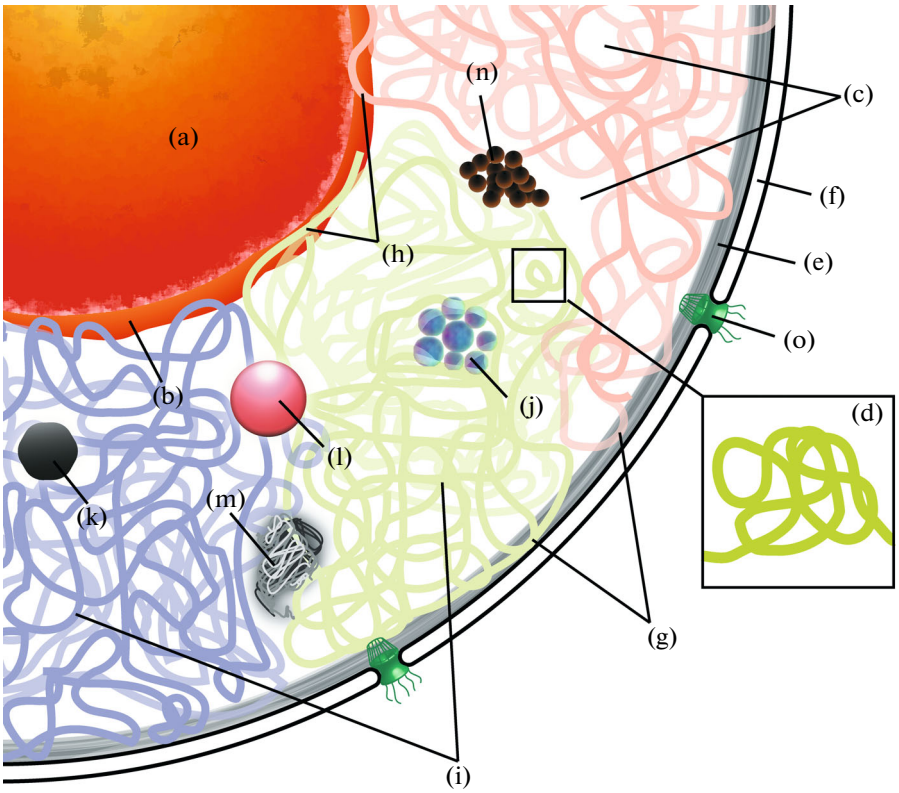

Fig. 1. Structure of the eukaryotic nucleus and main types of nuclear compartments (drawing). (a) Nucleolus, (b) perinucleolar space, (c) interchromatin domain, (d) topologically-associated domain, (e) lamina, (f) nuclear envelope, (g) lamina-associated domains, (h) nucleolus-associated domains, (i) chromosome territories, (j) Polycomb body, (k) insulator body, (l) PML body, (m) Cajal body, (n) nuclear speckles, and (o) nuclear pore complex.

by chromatin and the so-called interchromatin domain (Fig. 1c) [10, 11] are also distinct spatial compartments, although failing to match the above definition.

The interrelationships of gene activity, the spatial organization of chromosomes, and the functional compartmentalization of the cell nucleus are considered in detail in this review.

SPATIAL ORGANIZATION OF THE GENOME

General Principles of Chromosome Folding and Chromatin Domains

In the eukaryotic cell, an extremely long DNA thread (approximately 2 m of DNA per human haploid chromosome set) is packaged in a relatively small volume of the cell nucleus, which is usually about 10 μm in diameter. In spite of its multifold compaction, DNA is accessible for transcription and replication. The mechanisms of DNA packaging in chromatin have been a subject of intense research for the past 40 years. Several hierarchic levels are recognized in DNA compaction, and the first one consists in DNA wrapping around a histone octamer to produce a nucleosome [12]. A nucleosome chain folds further to produce presumably the so-called 30-nm fiber, which forms additional loops or other supercoiled structures. The nucleosome particle is the only characterized in detail among these structures [13]. The structure of the 30-nm fiber is still unclear [14], and even its existence in the living cell is questioned [15–19]. As for higher-order chromatin packaging, the available experimental data are so discrepant that it is infeasible to construct an integral picture for the spatial organization of the genome [19–21].

A principal difficulty was that there were no experimental techniques to study the DNA folding in intact nuclei. Substantial progress in understanding the spatial organization of the genome was made with the development of chromosome conformation capture (3C) technology [22], which is based on in situ ligation of closely spaced DNA fragments [23], and 3C-based genome-wide methods, such as high-throughput 3C (HiC) [24, 25]. Apart from reporting numerous examples of spatial interactions between distant regulatory elements, such as promoters, enhancers, and insulators [26–30], HiC made it possible to advance a globular model for genome organization [17]. The model suggests that the genome is divided into topologically isolated globular domains, which are termed the topologically associated domains (TADs) or just topologi-

cal domains (Fig. 1d). On average, the domains are approximately 1 Mb in human and mouse cells [31] and 100 kb in *Drosophila* cells [32]. The frequency of contacts between genome regions located in one topological domain is higher than between regions of different domains. The partitioning of the genome into domains is conserved among cells of different types within species and even among related species, such as human and mouse [31]. The conservation suggests an ancient evolutionary origin for the genome elements and mechanisms responsible for higher-order chromatin packaging. Topological domains are lost during mitosis and restored again in the interphase [33], indicating that special epigenetic mechanisms sustain the reproduction of large-scale spatial genome organization in both individual chromosomes and the cell nucleus through generations. The positions of topological domains correlate well with the positions of activating or repressive histone modification domains and lamina-associated domains (LADs, see below). However, the fact that topological domains are stable in cells differing in gene expression pattern and histone modifications (embryonic stem cells, brain cells, and fibroblasts) indicates that the domain structure is not governed by transcription or histone modification, but rather depends on certain intrinsic properties, which may be determined by the DNA nucleotide sequence, e.g., binding sites for universal protein factors [34]. Some differences in HiC interactions are still detectable between cells of different types, being usually related to genes subject to differential regulation. It is of interest that such facultative interactions commonly occur within one topological domain.

To understand what demarcates the topological domains, their positions were collated with the distribution profiles of insulator proteins and other epigenetic markers. In *Drosophila*, domain boundaries were enriched in DNase-hypersensitive regions and binding sites for the CP190 and Chromator insulator proteins, which are known to play a role in organizing the chromosome structure [32]. In mammalian cells, the boundaries of topological domains were enriched in housekeeping gene promoters and CTCF-binding sites. Yet only a minor portion of all CTCF sites was associated with domain boundaries. The other genomic elements observed at domain boundaries included tRNA genes and short interspersed repeats (SINEs), which may also be related to the insulator function [35, 36]. Note, however, that the topological domain structure could be determined not only by the specific boundary elements, but rather by within-domain interactions between particular regions. We think that these interactions play a key role in establishing and maintaining the topological domain structure, while domain boundaries are determined passively and have no structural function. A spatial interaction between DNA replication origins or closely spaced promoters of housekeeping genes can be considered as a possible determinant of the spatial organization of topological domains in this context.

Genome regions that interact with relatively stable nuclear structures are another class of chromatin domains. In particular, the nuclear lamina plays a role in fixing the chromatin domains (Fig. 1e). The nuclear lamina covers the nucleoplasmic surface of the inner nuclear membrane (Fig. 1f) and consists of the proteins lamins, which form extended polymeric structures [37, 38]. Maps of genome–nuclear lamina interactions provide information on the general spatial organization of interphase chromosomes. Approximately 1300 LADs having contacts with lamin B1 were identified in mammalian cells by DamID technology [39]. The LADs account for approximately 40% of the genome and are rather large, varying in size from 100 kb to 10 Mb (0.5 Mb on average) (Fig. 1g). Contacts with the nuclear lamina are tissue specific in part [40]. A domain character of interactions with the nuclear lamina was similarly observed in flies and worms [41–43]. The majority of genes located in LADs are transcriptionally inactive, indicating that the nuclear lamina is a repressive nuclear region [39–43]. In fact, a locus artificially attached to the nuclear lamina or internal nuclear membrane shows decreased transcriptional activity [44, 45], although exceptions are known [46].

The mechanisms that target extended DNA regions to and hold them on the nuclear lamina are still poorly understood. A certain role is possibly played by nuclear lamina-associated DNA-binding proteins that recognize specific nucleotide sequences. A recent study in human cells showed that $(GA)_n$ repeats are capable of targeting certain LADs to the nuclear lamina [47]. However, a systematic genome-wide analysis did not detect any enrichment in $(GA)_n$ repeats for LADs [39], indicating that the repeat-based attachment mechanism is not universal. Constitutive LADs (i.e., LADs that are invariant in cells of different lineages) overlap to a great extent with A/T-rich isochores in mammals [48]; i.e., A/T-rich DNA regions may play a role in anchoring genome segments on the nuclear lamina. Studies with a *Caenorhabditis elegans* model showed that histone methyltransferases MET-2 and SET-25, which methylate histone H3 at Lys9, act cooperatively to ensure a peripheral localization and silencing of transgenic repeats [49]. Contacts with the nuclear lamina were partly lost on a genome-wide scale in cells knocked out in both MET-2 and SET-25 genes. Thus, the interaction of genome regions with the nuclear lamina can be guided by both specific DNA sequences and chromatin modifications.

The nucleolus also provides a platform for spatial genome organization. The DNA fraction purifying with nucleoli upon their isolation was examined by two research teams [50, 51]. Apart from the expected rRNA gene loci, regions of almost all chromosomes were observed in the fraction. The regions, which were termed the nucleolus-associated domains (NADs,

Fig. 1h), contain predominantly repressed genes and are enriched in repressive chromatin modifications, in particular, trimethylation of histone H3 at Lys9. A substantial overlap was unexpectedly observed between LADs and NADs [50, 51], although data on cells of different types were used so far for the comparisons. It is possible that LADs and NADs consist, at least in part, of the same type of repressed chromatin, which is distributed more or less randomly between the lamina and nucleolus. The model is supported by the microscopic observation that some chromosome regions associated with the nucleolus in a maternal cell can move to the periphery of the nucleus in the daughter cells after mitosis [51, 52].

Genome-wide methods allow comprehensive investigation of the genome compartmentalization, from studying the linear distribution of proteins along chromosomes to constructing three-dimensional models of particular genome domains and whole genomes. However, it should be noted that the available mapping techniques operate with thousands or millions of cells and yield a picture averaged over the cell population. Yet specific long-distance interactions occur only in a minor portion of cells at a given time according to the majority of microscopic studies and, indirectly, HiC data [17, 53, 54]. The averaging over many cells blurs the resulting picture of chromatin domains. For instance, does a protein cover a particular chromatin domain in every cell of a population or in only some of the cells? Does a protein cover the domain entirely or partly in an individual cell? Fraser and colleagues [55] recently developed a modified HiC protocol to probe the spatial interactions in individual cells. Studies using the protocol showed that the domain organization on a megabase scale is similar between individual chromosomes, while higher-order chromosome structures vary among cells.

Chromosome Territories

Although compact mitotic chromosomes were described as early as 1882, it was unclear until the late 20th century what are they in the interphase. Cremer and colleagues [56, 57] were the first to assume that interphase chromosomes are not fully decondensed in the nuclear space because UV laser irradiation of a limited area of the nucleus was observed to damage only a few chromosomes (damage was detected in the subsequent mitosis). The majority of chromosomes remained intact, indicating that each chromosome occupies a limited part of the nuclear space in the interphase. The interpretation was fully confirmed by the results of staining individual chromosomes with chromosome-specific probes, which were obtained in the same lab [58–60]. Interphase chromosomes were found to occupy compact and, in the first approximation, nonoverlapping nuclear areas, which are separated by regions depleted or even free of chromatin. The regions were collectively termed the interchromatin domain (Fig. 1c), while the term chromosome territory was proposed for the area occupied by an individual chromosome (Fig. 1i) [60]. The observations were confirmed and augmented in further research [61–64]. The relative arrangement of individual chromosome territories within the nucleus became the subject of intense studies. Yet they failed to yield a simple rule that would describe the positioning of chromosome territories in the nuclear space, revealing only that gene-rich chromosomes tend to occur in the center of the nucleus, while chromosomes with a low gene content tend to occur at the periphery [60,61]. It is noteworthy that the position of a particular chromosome relative to the center of the nucleus substantially varies among individual cells. The nuclear position of a chromosome is usually characterized by the average distance from the center of its chromosome territory to the center of the nucleus. Yet it should be understood that deviations from the average distance are substantial [65].

Individual chromosome territories display a polar distribution of gene-rich and gene-depleted segments, the former occurring closer to the center of the nucleus and the latter being closer to the periphery of the nucleus within one territory [66, 67]. The interchromatin domain was thought to provide for transferring the transcription products from the nucleus into the cytoplasm and supplying "building blocks" for transcription, replication, and other processes related to the genome function. Active genes were expected to occur close to the periphery of their chromosome territory according to the model. However, the assumption did not receive experimental support [66, 68–70] apart from the observation that certain actively transcribed genes are looped out of their chromosome territory into the interchromatin domain [71–73]. At the same time, a sponge-like structure was demonstrated for chromosome territories with the interchromatin domain penetrating into their interior (Fig. 1) [69, 74]. Such a structure was assumed to form because chromosome territories are organized as a series of linked globular domains of approximately 1 Mb in size, which are embedded in the interchromatin domain [10, 11, 74–76]. The globular domains probably correspond to replication foci [75, 77, 78] and TADs identified in HiC experiments (Fig. 1d; see General Principles of Chromosome Folding and Chromatin Domains). Transcription presumably takes place in the perichromatin space at the boundaries of condensed chromatin domains [70, 79]. The available data [70] are insufficient to decide whether transcribed genes are scattered throughout the surface of condensed chromatin domains or clustered in certain regions of the perichromatin space (e.g., the regions between TADs).

The mechanisms that maintain the organization of interphase chromosomes in chromosome territories are poorly understood. It was believed initially that electrostatic repulsion between negatively charged

chromosome surfaces ensures the formation of the interchromatin domain [60]. However, it is unclear why the same repulsion does not disrupt a chromosome territory from the inside, given that the territory consists of negatively charged subunits. A filamentous nuclear skeleton (nuclear matrix) was assumed to maintain the organization of chromosomes into chromosome territories [80, 81]. Yet there is still no convincing evidence that such a skeletal structure exists in living cells [82]. Computer simulation showed that many properties of chromosome territories can be explained in terms of conventional polymer dynamics, in particular, Brownian motion and segregation of nonbound polymer chains as a result of topological constraints [83]. The model of chromatin fiber folding into a series of random chromatin loops explains not only segregation of chromosome territories, but also the experimental finding that the distance between two FISH probes is independent of the genomic distance between the probes when the latter exceeds 10 Mb [84, 85]. Given that loop parameters (size and density) may vary between gene-rich and gene-depleted regions, it is easy to understand why chromosomes (chromosome arms) with a high or low gene density differ in shape [86].

A dynamic character is inherent in the territorial organization of chromosomes. Chromosome territories, as well as individual domains within a territory, move continuously on evidence of vital cell staining [87–91]. In line with these observations, an analysis of the spatial configuration of individual chromosomes in single cells showed that the configuration substantially varies among cells [55].

FUNCTIONAL NUCLEAR COMPARTMENTS

Nuclear compartments are certainly a hot topic in studying the eukaryotic genome and its activities. The structures and functional roles of nuclear compartments have recently been reviewed in [4, 92–95]. We did not intend to review them again. Our focuses are the possible role nuclear compartments may play in maintaining the chromosome folding and, vice versa, the role the chromosome folding may play in positioning the nuclear compartments. From this viewpoint, the nuclear compartments are reasonable to divide into two categories, those that contain DNA and are directly related to DNA metabolism and those that are not functionally related to DNA metabolism, but form in the vicinity of certain genomic loci (as is the case with histone locus bodies) or recruit certain genomic loci (as in the case with Cajal bodies and speckles).

Nuclear Compartments (Bodies) Associated with DNA Metabolism

Replication factories. It is surprising that little is known about replication factories. Replication was convincingly shown to occur in a countable number of "spots" in the nucleus during all S-phase stages, and the spots were termed the replication foci [75, 96–99]. The number of replication factories functioning simultaneously reaches ~1500 in early S [100]. Pulse-labeling experiments showed that replication forks cluster in the centers of replication foci [101]. Then pulse-labeled DNA gradually moves to the periphery of replication foci, creating the impression that DNA is dragged through immobilized (still) replication complexes [101–103]. A correlation is detectable between replication foci, globular domains visualized in interphase chromosomes, and TADs [75, 77, 78, 104–106]. Replication foci were identified as stable structural units of interphase chromosomes that are maintained through consecutive cell divisions [107, 108]. Cook and colleagues [109] visualized the replication factories in nuclei by electron microscopy after removing chromatin. It was observed that a factory includes approximately 40 replication forks and is a dense body of 100–300 nm in diameter [109–111]. The replication factory size increased with the S-phase progress [110, 111]. Although published more than 20 years ago, the observations were not reproduced in independent studies, and it is still unclear whether the factories (clusters of replication complexes) persist in the absence of replication. Whichever the replication factory structure, a replication focus is apparently a chromosome domain consisting of several replicons. The replicons are probably close together in the linear DNA sequence. Hence, replication factories are unlikely to contribute to the interphase chromosome landscape by forming long-distance interactions between genome regions that are far apart (more than 1 Mb).

Transcription factories. Like replication, transcription occurs in a limited number of nuclear sites, as is evident from the focal arrangement of phosphorylated (active) RNA polymerase II and labeled nucleotides incorporated in newly synthesized RNA [112–115]. The sites are considerably fewer than transcribed genes at any time, indicating that a factory accommodates several genes at once and ensures their coordinated transcription. The three types of eukaryotic RNA polymerases are organized in separate transcription factories [116–119]. Ribosomal genes are transcribed in the nucleoli, where RNA polymerase I and its cofactors cluster in small (200–500 nm) fibrillar centers. During transcription, rDNA slides on the fibrillar center surface, while newly synthesized transcripts are released in the adjacent dense fibrillar component [116]. Transcription factories containing RNA polymerase II are of special interest in the context of this review. On average, a factory is approximately 70–80 nm in size by immunoelectron microscopy [118] and contains up to 30 molecules of elongating RNA polymerase II and nascent transcripts [118, 120]. There are eight polymerase molecules in a factory according to other estimates [121]. Gene relocation to the existing transcription factories is thought to

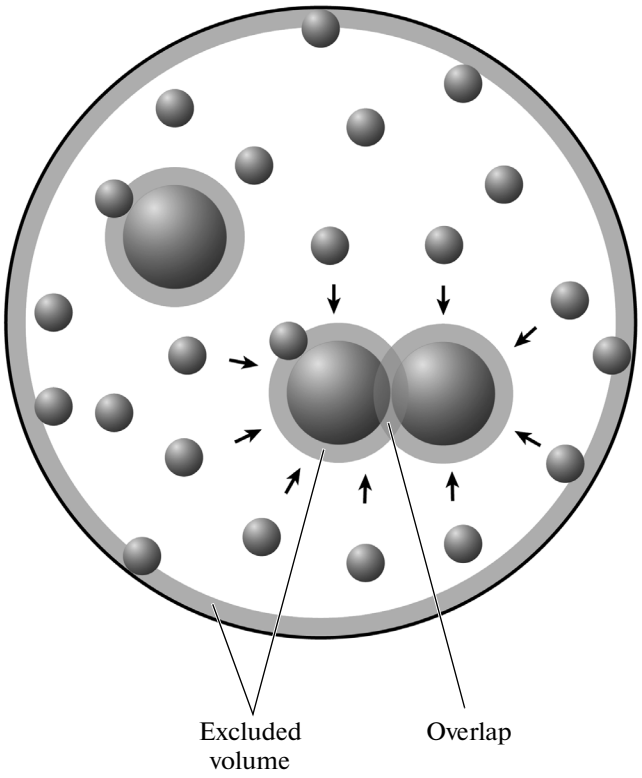

Fig. 2. Aggregation of large molecular complexes under macromolecular crowding. In high-concentration macromolecule solutions, small molecules (small spheres) move stochastically to continuously bombard large complexes (large spheres), thus facilitating their aggregation into still larger complexes. The aggregation generates an additional space for small molecule movements.

be an important step in transcriptional activation and is possibly controlled by special regulatory systems [114, 122–126]. The nature of the regulatory mechanisms is still unclear. Tissue-specific genes are presumably transcribed in specialized factories, which contain the necessary tissue-specific transcription factors [127–129]. Yet experimental findings do not perfectly agree with the specialized transcription factory model. For instance, a preferential association of erythroid-specific genes in factories containing the ELKF transcription factor was observed in erythroid cells [54], but only for no more than two erythroid-specific genes. A preferential association of more than two erythroid-specific genes in one transcription factory was not detected [54]. Given that a transcription factory contains up to 30 elongating RNA polymerase II molecules and the associated transcripts [118, 120], it is possible to assume that transcribed housekeeping genes mostly occupy the so-called specialized transcription factories. Although a certain preference in association with a given factory can be assumed for different genes transcribed with the same set of transcription factors [54, 130], the spatial proximity in the nuclear space plays a more important role in determining the genes that are to occur in one transcription factory [131]. It should be noted in this respect that an association in transcription factories is considerably stronger for genes belonging to one chromosome and especially to one chromosome arm than for genes belonging to different chromosomes regardless of their tissue specificity [54, 122, 130]. The probability for genes to occur in one transcription factory seems to depend on their nuclear positions and certain properties of the chromatin fiber (for more detail, see [115]). The situation where a higher colocalization frequency is observed for genes from different chromosomes is rather an exception, depending most likely on the specific spatial architecture of chromosome territories in cells of the given type [123]. There are data that transcription factories exist in the absence of transcription [121], but they are far from convincing. In fact, the conditions used to suppress transcription in [121] fail to ensure dissociation of elongating RNA polymerase II complexes. Preinitiation or elongating RNA polymerase II complexes already assembled could be held together as a result of molecular crowding (Fig. 2, see The Relationship between Nuclear Compartmentalization and Chromosome Folding below) [132, 133]. Their contact persists until large protein complexes are decomposed [115].

Polycomb bodies are repressive nuclear compartments known also as repressive hubs; they were studied most comprehensively in a *Drosophila* model (Fig. 1j) [134]. Although the term is used broadly, attempts to visualize the Polycomb bodies via correlative light electron microscopy did not meet with success [135]. Polycomb protein complexes clustering in a limited region of the nuclear space can be visualized by immunofluorescence, but they look like separate heterochromatin parts rather than individual nuclear bodies. Polycomb bodies are often considered to be aggregations of Polycomb repressive complexes bound to DNA [136, 137]. Yet Pirrotta and colleagues [138, 139] showed recently that an association of DNA with Polycomb complexes is insufficient for recruiting the corresponding genomic regions to Polycomb bodies. An important role in the process is played by insulators and, especially, the CTCF insulator protein [138–140]. In contrast, a linear arrangement of genes bound with Polycomb proteins can already provide for the Polycomb body formation [138, 139]. Like in the case of interactions between distant regulatory genomic elements, the chromosome organization in chromosome territories imposes certain limitations on the spatial interaction between targets of Polycomb proteins. DNA regions located in one chromosome arm are predominantly involved in this interaction. A highly dynamic character should be noted for Polycomb bodies. The pattern of gene contacts in Polycomb bodies varies among cells [138, 142]. The Polycomb protein exchange rate is extremely high in chromatin and, in particular, its fraction involved in Polycomb bodies [143, 144]. Thus, a dynamic balance between assem-

bly and disassembly of Polycomb bodies controls their occurrence in a given nucleus or a given region of the nuclear space.

Insulator bodies. Some of the *Drosophila* proteins important for the insulator function accumulate to produce foci in the nucleus [145]. The foci are known as insulator bodies (Fig. 1k) [146]. Such a distribution pattern was described for insulator proteins by many research teams [147–149], but its functional significance is still unclear. The association of insulators (i.e., complexes of insulator proteins with the corresponding DNA regions) in insulator bodies was initially believed to have a direct bearing on their function as regulatory elements of the genome [147, 150]. Yet more recent studies showed that insulator body assembly is not essential for the insulator function [151]. Insulator bodies are thought to act as depots to store the insulator proteins in the nucleus [151].

Nuclear Compartments (Bodies) Not Associated with DNA Metabolism

It is rather difficult to say how many DNA-free functional compartments are there in the nucleus. In fact, many nuclear proteins display a focal (nonuniform) distribution in the nucleus at least in some cells [152–155]. The most important compartments (PML bodies, Cajal bodies, speckles, and some others) are quite large and were identified by light or electron microscopy long before the advent of immunostaining (for more detail, see [2, 4, 93]). The compartments are in the interchromatin domain [10, 74, 156], and many of them are involved in primary transcript metabolism (splicing, end processing, posttranscriptional RNA modification, nuclear RNP assembly, etc.). Interestingly, the majority of the compartments have varying sets of protein components and are multifunctional, displaying enzymatic activities characteristic of different, often unrelated processes [4]. Many proteins accumulating in various nuclear compartments are essential for cell survival, but a vital role of their focal accumulation is questioned by several experimental findings (see below). Another fact to note is that some of the compartments occur exclusively in certain cells (e.g., cancer or rapidly proliferating cells). The number of compartments of a given type varies among individual cells. The best-studied nuclear compartments not directly associated with DNA metabolism are considered below.

PML bodies (known also as ND10 bodies or Kremer bodies) can be visualized by staining with antibodies against the PML protein (translocations involving its gene play a role in the development of promyelocytic leukemia). PML bodies are spherical in shape and vary in diameter from 0.1 to 1 μm (Fig. 1l). In addition to PML, which seems to serve as a platform for PML body assembly [157, 158]), more than 100 various proteins are found in PML bodies, sharing the only common property of being a target for sumoylation [92]. PML bodies are involved in the antivirus immune response, DNA repair, tumor growth suppression, gene expression regulation, proteolysis, telomere shortening, cell cycle control, senescence, and apoptosis [92, 159–161]. Tissue-specific contacts with certain genome loci were demonstrated for PML bodies [162–164]. Considering the multiplicity of functions ascribed to PML bodies [165], their nonuniform composition is not surprising. An association of PML with different protein sets can yield different PML bodies [166]. It should also be noted that a major portion of the nuclear PML pool occurs in a diffuse form, rather than accumulating in PML bodies [158]. PML bodies often degrade during virus infection [167–169] and in stress [161, 166, 170].

Cajal and histone locus bodies. Cajal bodies are nuclear compartments varying in shape and number per nucleus (Fig. 1m). The most important of their presumable functions are modifying small nuclear RNAs (snRNAs) and small nucleolar RNAs (sno RNAs) and assembling the corresponding RNPs [4, 94]. In addition, Cajal bodies contain factors responsible for the 3'-end processing of histone and other non-polyA mRNAs and factors maintaining the telomere integrity. Cajal bodies are associated with transcribed snRNA genes in cultured cells, which is possibly due to their binding with nascent transcripts [171–173]. The role Cajal bodies play in 3'-end processing of snRNAs and certain other non-polyA transcripts is related to the Integrator multiprotein complex contained in the bodies [174]. Telomerase was shown to accumulate in Cajal bodies [175, 176]. Cajal bodies are most likely involved in telomerase transport to telomeres [177].

Histone locus bodies are highly similar in composition to Cajal bodies. In particular, the compartments contain coilin, which is considered to be characteristic of Cajal bodies. Histone locus bodies are assembled at actively transcribed histone genes, but their function is not related to regulating histone gene activity. Their main function is the 3'-end processing of histone mRNAs [94, 178]. Histone locus bodies are virtually indistinguishable from Cajal bodies in amphibian oocytes; the only difference is that the former are associated with histone genes, while the latter are freely suspended in the nucleoplasm [178, 179]. Given that proteins and RNPs contained in histone locus bodies (Mxc, FLASH, Mute, and U7 snRNP) are involved in processing the 3' ends of histone mRNAs, the substrate (nonprocessed histone mRNAs) could be expected to nucleate body assembly. It was found in contrast to this assumption that a short regulatory DNA element occurring in the bidirectional promoter of the histone H3 and H4 genes suffices to induce assembly of minimal histone locus bodies (the so-called protobodies, which contain only part of the proteins found in functional bodies). Protobodies are assembled even in the absence of histone gene transcription [180]. However, another study of de novo

assembly of nuclear bodies showed that various Cajal body components (be they structural components, such as coilin, or functional components, such as snoRNPs or snRNAs specific to Cajal bodies) should be recruited to certain chromatin regions as an essential prerequisite to starting assembly of functional Cajal boies [181].

Although the proteins contained in Cajal and histone locus bodies are important for cell survival, it is unclear whether their accumulation in certain nuclear compartments is necessary for their functions. First, Cajal bodies do not occur in all cells of rapidly proliferating populations [182]. Cajal bodies are absent from the nuclei of certain differentiated cells in adult tissues [183]. The number of Cajal bodies in the nucleus seems to correlate with the intensity of snRNP biogenesis [184, 185]. Interestingly, a mutation of the gene for coilin, which is a main structural component of Cajal bodies, is not lethal in flies [186]. The mutants are fertile, though lacking Cajal bodies, and their snRNAs still undergo the modifications that normally occur in Cajal bodies [187]. Cells cultured from tissues of mice with a null mutation of the coilin gene harbor the so-called residual Cajal bodies, which contain various combinations of proteins found in normal Cajal bodies [188, 189]. Moreover, specific compartments detected in some of the cells contain Cajal body-specific proteins, e.g., SMN (survival motor neuron), which is a typical component of Cajal bodies [190, 191]. In some cases, SMN accumulates in specific compartments known as the gemini of Cajal bodies [192, 193]. Many proteins described as components of Cajal bodies are similarly found in PML bodies and nucleoli [194].

Nuclear speckles are specific compartments that harbor components of the splicing system (various snRNAs, SC35, and other spliceosome components). The compartments were initially known as the interchromatin granule clusters [195, 196] or SC35 domains [197]. Speckles are localized in the interchromatin domain [10, 74, 196], are irregular in shape, and vary in size (Fig. 1n) [197–199]. The speckle distribution pattern depends on the transcriptional status of the cell. An analysis of the nuclear speckle proteome revealed approximately 150 proteins with known functions, of which 80% were related to RNA posttranscriptional modification [200, 201]. In addition, lamins, various transcription factors, and proteins involve in mRNA exports are found in speckles [202–204]. It is commonly thought that speckles serve to temporally store the splicing components [95, 199, 205]. However, speckle destruction suppresses the splicing [206], indicating that speckles are not merely a store of splicing factors, but rather act as reaction centers where RNP complexes involved in splicing undergo maturation and assembly. Splicing occurs cotranscriptionally according to current views and, therefore, should take place in the perichromatin space. However, certain actively transcribed genes are found in the vicinity of nuclear speckles [207–211]. This localization presumably facilitates the recruitment of splicing factors to actively transcribed genes. Thus, nuclear speckles potentially play an important role in spatial organization of euchromatic regions [211]. Some authors think that nuclear speckles act as reaction centers (hubs) where transcription, splicing, and mRNA export are coordinated. A model was advanced that genes are recruited to speckles, transcription and splicing occur within the speckles or close to their surface, and the resulting mRNA passes through the internal speckle space and is directed to the cytoplasm [212].

RELATIONSHIP BETWEEN NUCLEAR COMPARTMENTALIZATION AND CHROMOSOME FOLDING

It is clear that functional organization of the cell nucleus is closely associated with spatial organization of the genome [5–8, 213]. DNA recruitment to transcription factories is often thought to affect the shapes of interphase chromosomes and to provide a means for establishing interchromosome contacts [54, 114, 115, 123, 125, 126, 214, 215]. As already mentioned, a similar role is possible for the other DNA-free compartments that are capable of recruiting certain genes (PML bodies and nuclear speckles) [162–164, 207–211]. A model popular a while ago postulated that the positioning of nuclear compartments is mediated by their recruitment to the nuclear skeleton (nuclear matrix) [216, 217]. Nuclear compartments anchored in this stable structure could provide landmarks for the positioning of interphase chromosomes and chromosome domains. Although the model is attractive, the available experimental findings are insufficient for it to be more than speculative. The nuclear matrix is to a great extent an elusive structure. Its existence in living cells is still unproved [82]. Even if the nuclear matrix does exist, many efforts will be necessary to explain how the nuclear compartments are positioned. Interactions of DNA regions with the nuclear lamina are still the only example where certain chromatin domains are anchored on a positionally stable nuclear structure (Fig. 1g). The interactions probably contribute to the proper radial positioning of inactive and active segments of interphase chromosomes. However, a filamentous structure similar to the cytoskeleton is absent from the interior of the nucleus. Moreover, while nuclear speckles were characterized as quite stable structures whose positions within the nucleus remain unchanged for hours [205, 218], PML and Cajal bodies diffuse in the interchromatin space as freely as an artificial inert entity of the same size [219]. Data are accumulating that the ordered organization of the eukaryotic nucleus is a product of balanced effects of various forces, in particular, the forces due to macromolecular crowding (Fig. 2) [132, 220–222]. It is clear that the interplay of various processes occur-

ring in the nucleus at a given time guides both chromosome folding and the spatial compartmentalization of the cell nucleus [7, 222–224].

To obtain an integral picture of this complex organization, it is necessary to consider the mechanisms that sustain assembly of nuclear compartments. It should be noted in this respect that all of the above nuclear compartments lack many properties characteristic of regular structural entities. They vary in shape, size, and number in the cell and may be absent from some cells, even from a fraction of cells cultured in one Petri dish. Compartments of the same type (e.g., Cajal or PML bodies) may contain different protein ensembles and perform different, sometimes unrelated, functions. The majority of proteins found in nuclear bodies occur in the nucleoplasm as well, and the rate of protein exchange between the nucleoplasm and bodies is rather high. Taken together, the observations indicate that stochastic processes play a substantial role in assembly [220, 225, 226].

The concentration of macromolecules in the eukaryotic cell nucleus is so high that assembly of nuclear compartments may proceed via self-organization and obey the laws describing the behavior of molecules and their complexes in high-concentration solutions [132, 220, 221]. Large entities tend to aggregate to produce even larger complexes in these conditions, creating an additional space for small molecules moving stochastically. Small molecules continuously bombard large complexes on many sides, thus supporting their integrity (Fig. 2) [133, 220, 224, 227, 228]. Forces acting under macromolecular crowding are assumed to play an important role in stabilizing the nuclear compartments or bodies, and the assumption has experimental support [221, 224]. Hence, nuclear bodies are sometimes considered to be transient, entropically advantageous macromolecular complexes in the congested nuclear space [222, 229]. It was even assumed that nuclear bodies play no role and that only the enzymes and proteins occurring in the bodies are essential [230]. There are observations indeed that disruption of nuclear bodies by knocking out their important structural components (such as coilin in the case of Cajal bodies [186, 187]) has no effect on the cell viability provided that components of the disrupted bodies remain in the nucleoplasm. However, gathering the proteins involved in one process together in nuclear bodies could be advantageous in special conditions (rapid proliferation, stress, etc.). The issue deserves further investigation.

Although nuclear bodies have some properties of stochastic conglomerations of proteins and their complexes, the protein sets from nuclear bodies of different types overlap only in part. The forces acting under molecular crowding can explain the stability of macromolecular ensembles, but not the specificity (or partial specificity) of their composition. It is possible to think that the proteins combined in a particular nuclear compartment have affinity for each other or for a structural component essential for assembling compartments of the given type. The latter assumption better agrees with experimental findings [231]. Coilin and PML are necessary for assembling Cajal and PML bodies, respectively [157, 186], and the finding agrees with the assumption that the proteins provide a platform for nuclear body assembly. In addition, noncoding RNAs can act as an assembly platform, as is evident from studies of paraspeckles (yet another type of nuclear bodies with an unclear function) [232]. Various Cajal body components immobilized in a preset chromatin region were shown to initiate assembly of a functional Cajal body [181]. At first glance, the observation supports the idea that various Cajal body components have affinity for each other. However, if affinity for coilin is characteristic of all of the Cajal body components, then any of the components should recruit coilin, which, in turn, should recruit all other components, eventually resulting in a functional Cajal body. Several models were advanced to describe assembly of nuclear bodies, including consecutive (ordered) assembly, stochastic assembly, and seeding of nuclear bodies [2, 93]. The last model agrees best with experimental finings. The model postulates that a special seeding event (like a crystallization center appearing in a solution) should occur to initiate assembly of a nuclear compartment. Assembly does not follow any special order [93, 233]. A seeding event can be related to the function of the given compartment. As was shown using in vivo fixation, an accumulation of several coding and noncoding RNAs in a certain region of the nucleus initiates assembly of various nuclear compartments that serve for the maturation of these RNAs [234]. Transcription was concluded to be the force that drives the formation of nuclear bodies. Accordingly, primary transcripts were assumed to provide a framework for nuclear bodies of various types to form around [234, 235].

The most interest question in the context of this review is how the spatial organization of interphase chromosomes is related to the functional compartmentalization of the cell nucleus. The idea that chromosome folding guides the nuclear compartmentalization seems at first glance to contradict the idea that the interaction of genomic loci with nuclear compartments is necessary for a specific architecture of interphase chromosomes, but this is not exactly so. Both of the ideas are, in fact, correct. While a basal compartmentalization of the nuclear space, including the formation of the interchromatin domain, is guided by the territorial organization of chromosomes, the interactions of individual chromosome loci with each other in the interior or on the surface of nuclear compartments play an important role in guiding the chromosome structure. Assuming that an internal skeletal structure, such as the nuclear matrix [82], is absent from the nucleus, the chromatin fiber network can be assumed to provide a structural basis for nuclear compartmentalization [5–8, 213]. Segregation of interphase chro-

mosomes and the consequent formation of chromosome territories (Fig. 1i) can be explained in terms of physical properties of charged polymers [83–86]. The formation of channels within chromosome territories is less clear. We think that repulsion between topological domain surfaces plays a key role in the process. The surface of a domain may have a greater charge as compared with its interior. This asymmetric charge distribution within a topological domain possibly arises because transcriptionally active chromatin regions, which are known to be rich in hyperacetylated histones, tend to occur at the domain surface. The negative charge of DNA is partly neutralized as DNA associates with positively charged histones. The positive charge of histones is lower in transcriptionally active regions because their histones are extensively acetylated. Hence, the topological domain surface (where transcriptionally active regions predominantly occur, see Chromosome Territories) should have a greater negative charge as compared with interior regions. This charge distribution may prevent the topological domains from interfusion and facilitate the formation of interchromosomal channels. Taken together, the above findings indicate that physical factors are mostly responsible for the general landscape of nuclear compartmentalization [83, 223, 236, 237]. Once established after mitosis, the territorial organization of interphase chromosomes is stabilized by the interactions of certain regions with the nuclear lamina and perinucleolar compartment. The nucleolus is the main nuclear compartment, and its positioning in the nucleus is apparently guided by the spatial organization of the chromosomes that harbor active nucleolus-organizing regions. Heterochromatic regions of various chromosomes are anchored in the perinucleolar and peripheral nuclear layers (Fig. 1), and interconnected chromosome domains form as a result, providing a structural basis (chromatin framework) for nuclear compartmentalization. The chromosome domains remain highly dynamic. Their structure can be further modulated as inter- and intrachromosomal contacts are established. An association of different genomic loci within a functional nuclear compartment must play an important role in the process. We think that compartments start forming around certain genomic regions as a result of functional activity of the regions (e.g., to process the newly synthesized transcripts [234, 235]). Microcompartments originating in different sites may then fuse to produce functional nuclear bodies owing to affinities of their components and the forces arising under macromolecular crowding. The genome regions associated with the microcompartments will therefore remain spatially close to each other as long as the processes that have initiated microcompartment assembly continue. The probability for two genome regions to be involved in organizing a nuclear body is determined primarily by their initial spatial proximity because movements of genome loci and protein complexes bound to them are only local and obey the laws of Brownian motion [89, 238–241]. Although certain findings indicate that active transport of genome loci or total chromosome territories is possible in the nuclear space and involves actin–myosin motors [242–246], the assumption still lacks sufficient experimental support. Thus, it is questionable if such a transport mechanism is universal in the nucleus.

The frequency at which regulatory elements are brought together within or close to a nuclear compartment can be modulated by various factors, as assumed, for instance, for tissue-specific genes recruited to one transcription factory [54, 241]. At the same time, the nuclear organization as a whole and the total set of contacts between distant genomic elements (the so-called interactome) are highly dynamic and stochastic by their nature. A typical configuration of an interphase chromosome is determined by a balance of several possible configurations [55]. Thus, an ordered character of nuclear organization results from a chain of stochastic events, and little is predetermined in the establishment of this character.

CONCLUSIONS

The spatial organization of interphase chromosomes and the functional compartmentalization of the cell nucleus were studied separately for a long time. It becomes clear now that the two problems are closely related. Eukaryotic chromosomal DNA packaged in chromatin most likely provides a structural basis for the spatial compartmentalization of the cell nucleus and assembly of functional compartments. A highly dynamic character should be emphasized for chromosome folding and the functional compartmentalization of the cell nucleus. Chromosomes can assume many alternative configurations on evidence of fluorescence in situ hybridization [54, 247] and HiC analysis [55], and nuclear compartments are continuously assembled and disassembled, as is evident from the high exchange rates of their components [248]. Thus, the order is to an extent illusive in the eukaryotic cell nucleus, arising from stochastic events and being based on a continuous selection among a variety of possibilities, which provide for rapid adaptation of the genome function to changing environmental conditions.

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