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REVIEW

Structural–Functional Domains of the Eukaryotic Genome

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Abstract—It is well known that DNA folding in the eukaryotic cell nucleus is tightly coupled with the operation of epigenetic mechanisms defining the repertoires of the genes expressed in different types of cells. To understand these mechanisms, it is important to know how DNA is packaged in chromatin. About 30 years ago a hypothesis was formulated, according to which epigenetic mechanisms operate not at the level of individual genes, but rather groups of genes localized in structurally and functionally isolated genomic segments that were called structural and functional domains. The question of what exactly these domains constitute has been re-examined multiple times as our knowledge of principles of chromatin folding has changed. In this review, we discuss structural and functional genomic domains in light of the current model of interphase chromosome organization based on the results of analysis of spatial proximity between remote genomic elements.

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The question of existence of structural and functional domains in the eukaryotic genome that are targets for the action of regulatory mechanisms has been discussed in the literature for many years. The discussion began after the discovery of differential sensitivity of long genomic regions to DNases [1] and was further developed after the discovery of the locus control region of the β-globin gene domain [2, 3]. The formulated domain model of eukaryotic genome organization postulated that the experssion of one or several gene(s) can be controled by changing the chromatin folding pattern of a long genomic region – the domain where these genes are localized [4, 5]. The length of such domains was supposedly limited by matrix attachment regions or by specific genomic elements – insulators [6]. It should be noted that the domain model of genome organization was based on the results of studying the vertebrates β-globin gene domains and some other genomic domains, which are now usually referred to as domains with distinct boundaries [6, 7]. The increase in the number of characterized genomic domains in the epoch of whole genome sequencing has shown that organization of the domain of β-globin genes in vertebrates is unique rather than typical of the genome in general. Most of the tissue-specific genes are surrounded by continuously expressed ("housekeeping") genes and, hence, such genes are the components of transcriptionally active (DNase-sensitive) chromatin in cells of different lineages. As an example, one can mention the domain of α-globin genes in vertebrates whose major regulatory element is located in one of the introns of the housekeeping gene situated upstream to the domain [8]. It is clear that the domain model of eukaryotic genome organization based on the hypothesis that activation of tissue-specific gene transcription requires cardinal chromatin reconfiguration in the long genomic region [9] cannot be used for describing the regulatory mechanisms of the domain of α-globin genes and other similar domains. Considering the fact that such domains are predominant in the genome, one can state that the domain model of eukaryotic genome organization has lost its revance in the original version. At the same time, research results suggest that animal genomes contain structural and functional domains of a different type, which restrict the area of enhancer activity. Being originally identified by functional tests, these domains were named regulatory domains, landscapes, or archipelages [10-12]. They were demonstrated to coincide with the topologically associating chromatin domains identified in the study of three-dimensional genome organization in the cell nucleus [11, 13-15]. This review is devoted to the modern concepts of chromatin packaging in the cell nucleus and dicussion of the role of three-dimensional genome organization in the regulation of gene activity.

Abbreviations: eRNA, enhancer RNA; Hi-C, high-throughput chromosome conformation capture; TAD, topologically associating domain.

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HIGHER LEVELS OF CHROMATIN PACKAGING IN THE CELL NUCLEUS

For many years it was generally accepted that there was a certain hierarchy of the levels of DNA packaging in chromatin [16]. The first two levels of packaging – DNA wrapping around nucleosomal globules, with formation of the so-called 10-nm chromatin fibril, and subsequent folding of this fibril into a 30-nm fibril – seemed to be most comprehensible. Regarding the next level of chromatin packaging, the opinions of different researchers were at variance with each other. One of the popular models postulates that the 30-nm fibril is arranged into extended (50-250 kb) loops fixed at the nuclear matrix [16, 17]. Then they postulated the existence of loop clusters containing ~2500 kb DNA and forming chromomeres that can be observed in the meiotic prophase [18]. Another model postulated that the 30-nm fibril is coiled into several hierarchic solenoids [19, 20].

In recent years, the existence of a 30-nm chromatin fibril in living cells was questioned [21-25]. The novel methodological approaches have not shown any regular 30-nm fibrils in cell nuclei. Chromatin masses seemed to consist of densely associated nucleosomal filaments (10-nm fibrils). The densities of nucleosome packaging in the euchromatin and heterochromatin regions were different; however, no regular supernucleosomal structures have been found [25-27]. These results are in good agreement with the observations of other authors, who have demonstarted that the density of DNA packaging, even in the transcriptionally acitve chromatin fraction, substantially exceeds the density that can be reached through formation of a 30-nm fibril [28]. At present, most authors agree that there are no regulary supernucleosomal structures in the nuclei of living cells. At the same time, DNA is packaged through association of nucleosomal filaments with the formation of various types of aggregates. Under certain conditions, this process can be easily simulated *in vitro* [29].

Studies employing the so-called C-methods based on the analysis of physical closeness of different parts of the genome in the three-dimensional space of the cell nucleus have made a substantial contribution to understanding the principles of chromatin packaging. These techniques are based on the proximity ligation procedure [30]. The most informative method for analyzing the general principles of chromatin packaging is the Hi-C technique (high-throughput chromosome conformation capture), which allows analysis of the physical proximity of different DNA fragments on the whole-genome scale [31]. This experimental approach allowed to demonstrate the spatial segregation of active (A) and inactive (B) compartments in mammalian chromatin, which correspond to euchromatin and heterochromatin in the first approximation [31]. The analysis of higher-resolution Hi-C maps showed the presence of topologically associating domains (TADs) (Fig. 1). The main property of TADs is that spatial contacts between genomic elements are established much more frequently within a TAD than between the TADs [32-34]. The TADs and chromatin compartments have been found in mammals [32, 33], insects [34, 35], and birds [36]. Some contact domains can also be revealed in the genomes of plants and lower eukaryotes [37-40]. However, they are substantially different from the TADs of mammals and *Drosophila* both in size and in the levels of insulation and genome coverage. In original works, it was emphasized that the profiles of chromosomes partitioning into TADs are rather conservative both between the cells of different lineages and within the syntenic regions in closely related species [32, 41, 42]. However, this conservatism is limited [34, 43]. The profiles of chromosome partitioning into TADs are substantially different, inter alia, due to the differences in transcription profiles typical of specialized cells [43]. It should be noted that TADs per se are arranged hierarchically, i.e., may include several levels of smaller contact domains separated by weaker boundaries [43-45] (Fig. 1). The higher-resolution Hi-C maps have shown that mammalian TADs include contact subdomains, most of them being chromatin loops with CTCF-binding sites at their bases, where cohesin enrichment is detected

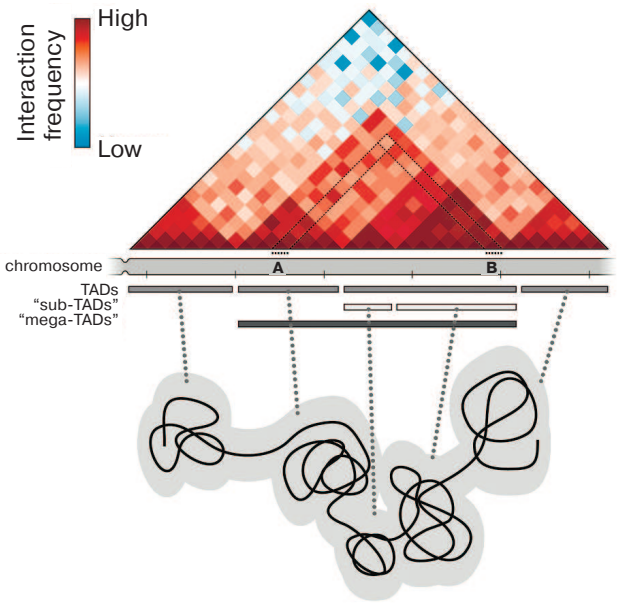

Fig. 1. Chromosome organization into topologically associating domains. The contact map of a hypothetic genomic region is shown, and the annotation of TADs for this region demonstrates the presence of several hierarchic levels of domains. Each pixel (rhombus) on the contact map indicates the total number of contacts of the respective chromosome regions expressed in colors, from blue (few contacts) to dark red (many contacts). For example, the number of contacts between chromosome regions A and B is shown by the pixel marked with the black dotted lines. TADs are usually interpreted as chromatin globules, as is shown schematically in the lower part of the figure.

[46]. The question as to the domains of which level should be referred to as TADs is still under discussion and answered differently [41, 43]. Most authors believe that the TADs of mammalian cells are one to several millions of base pairs in size [32, 33, 41], while the average size of TADs in *Drosophila* is hundreds of thousands of base pairs [34, 47]. At the same time, it should be noted that TADs can be distinguished from the contact domains of other levels by functional (the correspondence to replication-timing domains [48] and regulatory domains [11]) rather than structural criteria [49]. In a recently published work by Rowley et al. [35], the existence of TADs in the *Drosophila* genome is disputed. Those authors believe that the major structural units of *Drosophila* chromosomes are the compartments that may vary in length from several kilobases to several hundreds of kilobases [35].

The physical nature of TADs is not quite clear. They are usually interpreted as chromatin globules that can be visualized by different microscopic techniques [50-52] (Fig. 1). This interpretation is confirmed by the results of hybridization *in situ* with the samples distributed along an individual TAD [53-55]. It should be mentioned that microscopic techniques make it possible to analyze single cells, whereas biochemical methods have been used until recently only for cell population analysis. It is clear that the analysis of populations can reveal only some general regularities. It creates certain difficulties in the direct comparison of results obtained by microscopic and biochemical approaches. The problem can be partially solved by averaging the microscopic observations of a great number of cells. In particular, this approach applied to the analysis of the super-resolution microscopy images allowed to confirm the existence of active and inactive chromatin compartments revealed by analysis of the contact maps of genomic interactions [55]. On the other hand, the experimental protocols developed in recent years allow construction of Hi-C maps of spatial genome organization in single cells [56-58]. The results obtained using these protocols can be directly compared with the data of super-resolution microscopy and altogether demonstrate good agreement between observations in both approaches [59]. Among the conceptually important results, it should be noted that the genomic positions of TADs in single cells do not always coincide with the positions of "statistically average TADs" predicted by population data analysis [58]. Another important observation made during the Hi-C analysis of single cells is that the same TAD may adopt different configurations, beginning from a highly extended stretch to a completely condensed globule [60]. Both observations are indicative of the dynamics of chromatin fibril and considerable variability of spatial organization of separate genomic segments in single cells.

TOPOLOGICALLY ASSOCIATING DOMAINS ARE FUNCTIONAL UNITS OF THE GENOME

According to the almost universally accepted model, an enhancer can activate a gene only if it contacts the promoter of the gene. Most enhancers are located at a

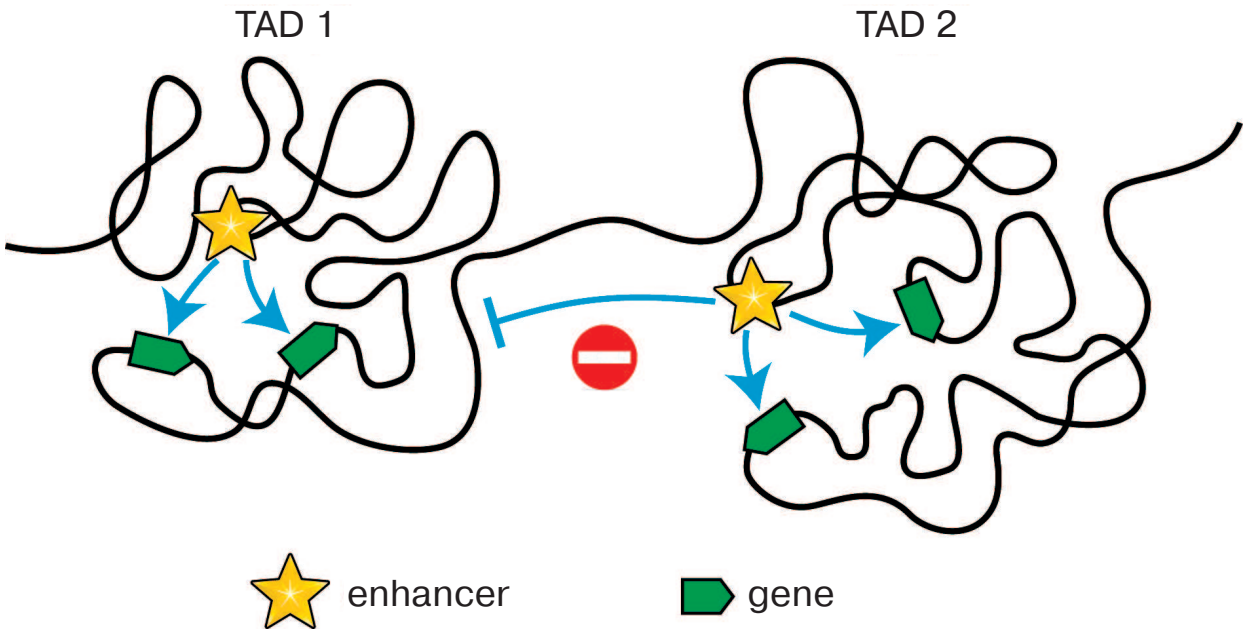

Fig. 2. Restriction of the scope of activity of enhancers by topologically associating domains. Localization within the same TAD increases the probability of spatial contacts between the enhancer and the controlled promoters. On the contrary, localization in different TADs prevents communication between "wrong" partners.

considerable distance from the genes they activate. Accordingly, for promoter activation, an enhancer must contact this promoter via looping of an intervening DNA segment [61] (see below Fig. 3). The existence of such spatial contacts between remote enhancers and promoters can be really found by both biochemical (Hi-C and other C techniques) and microscopic (fluorescent *in situ* hybridization) approaches [62-66]. The significance of enhancer–promoter communication for transcription activation has been directly demonstrated in experiments on forced chromatin looping [67]. Spatial contacts between remote genomic elements are established mostly inside the TADs. Thereby, TAD bounadires must restrict the scope of enhancer activity as has been demonstrated in some studies [11, 68, 69] (Fig. 2). The fusion of TADs due to deletion of the intervening spacer region leads to changes in scope of enhancer activity, which in some cases results in emergence of various pathologies due to the impaired regulation of gene expression within the fused TADs [13-15]. All these results show that TADs are the structural and functional genome units playing the key role in the work of transcription regulation systems. That is probably why the profile of chromosome partitioning into TADs is conservative within syntenic regions in different biological species [32, 41, 42]. In addition to restriction of the scope of enhancer activity, the chromosome partitioning into TADs reduces the time necessasry for establishing enhancer–promoter communication. Eukaryotic cells have no mechanisms providing the directional movement of the enhancer toward the promoter. The local movements of different regions of the chromatin fibril are stochastic due to the energy of thermal motion of molecules [70]. The establishment of enhancer–promoter communication will depend on how soon the enhacer and the controlled promoter will meet in the nuclear space. It has been experimentally determined that a certain randomly chosen genomic locus can examine 0.5-0.8 μm in 1 h [71]. Restriction of the search area by an individual TAD (Fig. 2) undoubtedly shortens the time needed for establishing the enhancer–promoter communication. In this context, it is essential that the TAD structure is not rigid. Inside the TAD, there is a continuous alternation of chromatin configurations [60, 72].

With reference to functional genome units, it would be wrong to consider only the transcriptional regulatory domains. Replication domains play a key role in the work of the eukaryotic genome. Such domains include replicons and replication time zones. The profile of replicons is rather dynamic and varies from cycle to cycle due to the presence of a considerable number of alternative replication origin regions in eukaryotic genomes [73]. On the other hand, DNA replication time zones are sufficiently stable in each particular type of cells [74]. Several researchers have demonstrated a strong correlation between these zones and TADs [48, 75].

MECHANISMS OF TAD FORMATION

The ability to form various compact structures is a basic property of nucleosomal fibrils. This ability is determined by the possibility of establishing electrostatic interactions between the positively charged *N*-terminal domains of histones (especially histone H4) and the negatively charged domain on the surface of nucleosomal globules [29, 76]. Experiments *in vitro* have demonstrated that at low chromatin concentrations the interactions occur mainly between nucleosomes within the nucleosomal chain, with the formation of a 30-nm fibril [77, 78]. At high chromatin concentrations, the interactions more commonly occur between the nucleosomes of different chains (or different regions of the same chain), resulting in the formation of various condensed structures. The ability to establish electrostatic contacts between nucleosomes is controlled by the levels of histone acetylation. At high levels of acetylation, the positive charge of histone *N*-terminal domains decreases and, hence, the opportunity of establishing internucleosomal contacts is lost [79, 80]. The high level of histone acetylation is typical of active chromatin. In *Drosophila*, active genes are localized mainly between the TADs, while inactive genes are localized inside the TADs [43]. We have demonstrated by computer modeling that a chromatin fibril composed of alternating active and more extended inactive regions is folded into compact globules (TADs) containing mostly inactive chromatin separated by less compact regions (inter-TADs) containing mostly active chromatin [43]. It is clear that the TADs formed thereby have functions in the storage of repressed genes. Indeed, by comparing TAD profiles in different cell lines, we have demonstrated that the activation of transcription of tissue-specific genes correlates with the decompaction of TADs and in some cases leads to the emergence of new inter-TADs [43]. TADs must have more complex organization to play the role of functional domains of the genome, which is typical primarily of TADs in mammalian chromosomes. The architectural proteins that can arrange the genome into loops play a key role in establishment and maintenance of this organization. In mammals, CTCF and cohesin play the key role in the contacts between remote genomic elements [81-84]. As noted in some works, CTCF and cohesin are localized preferentially at TAD boundaries [32]. Moreover, deletions of CTCF-binding sites at TAD boundaries result in the weakening of TAD insulation and, in some cases, in the fusion of neighboring TADs [13, 85-87]. The inhibition of experssion and induced degradation of CTCF have the same effect [88, 89].

Although when discussing the role of CTCF and other architectural proteins in spatial genome organization the emphasis is often placed on the ability of these proteins to make loops [90, 91], chromatin loop formation per se cannot lead to the appearance of a topologi-

cally associating domain, within which the spatial contacts between remote genomic elements are preferentially established. Chromatin loop formation guarantees only preferential spatial interactions between the chromatin segments localized at the loop base. For explaining the mechainsm of TAD formation, it has been postulated that there is a continuous processive looping of different chromatin segments within a region limited by convergent CTCF-binding sites. At the same time, looping may begin at random sites, and the period of loop existence is limited. This model termed "the mechanism of loop extrusion" [92] and confirmed by the results of computer modeling provides a rational explanation for quite a number of experimental observations [87, 92, 93]. The model postulates the existence of a certain molecular motor supporting DNA looping. Some indirect evidence suggests that cohesins perform the function of a motor [92-94]. However, the DNA-looping ability of cohesins has not been demonstrated directly. The nature of the extrusion motor, as well as the nature of loop-bordering insulator, is not fundamentally important for the loop extrusion model. For example, the anchored RNA polymerase molecules can function as extrusion motors [95]. As for the restrictive element that prevents loop spreading, its function can be performed, in addition to CTCF-binding sites, by promoters or some noncanonical DNA structures.

TAD organization as a series of dynamic (appearing and disappearing) chromatin loops must favor the reduction of time necessary for that contact between different regions of chromatin fibrils within a TAD, because scanning in this case will be performed in not three- but in one-dimensional space (along the DNA strand).

INVOLVEMENT OF NONCODING RNA IN SPATIAL GENOME ORGANIZATION

The results of some works show that enhancers are brought to the controlled promoters with either direct or indirect involvement of enhancer RNA (eRNA) transcribed on either side of the enhancer [95-97]. The particular role of eRNA in enhancer–promoter communication is yet to be investigated. According to one of the scenarios (Fig. 3), eRNA can maintain contacts between the enhancer and the Mediator coactivator complex. Indeed, for some noncoding RNAs transcribed from enhancers (noncoding activator RNA, ncRNA-a) it has been demonstrated that their ability to stimulate transcription depends on the interaction between such RNAs and components of the Mediator coactivator complex. At the same time, a chromatin loop was formed between the enhancer, from which ncRNA-a is transcribed, and the activated gene. Deletions of both ncRNA-a and Mediator components impaired chromatin loop formation and suppressed the ability of the enhancer to activate the controlled gene [98, 99]. It is interesting that the architectural protein CTCF also binds a broad range of noncoding RNAs on the whole-genome scale [100, 101]. CTCF contains an RNA-binding domain at the *C*-end, and CTCF multimerization probably important for DNA looping [102] depends on the presence of RNA [101]. Moreover, recently it has been shown that YY1 – the universally expressed transcription factor that is bound to CTCF [103] and enriched at the base of the DNA loops [46] – is also bound to RNA, thereby increasing the affinity of this factor to its binding sites in the genome [104].

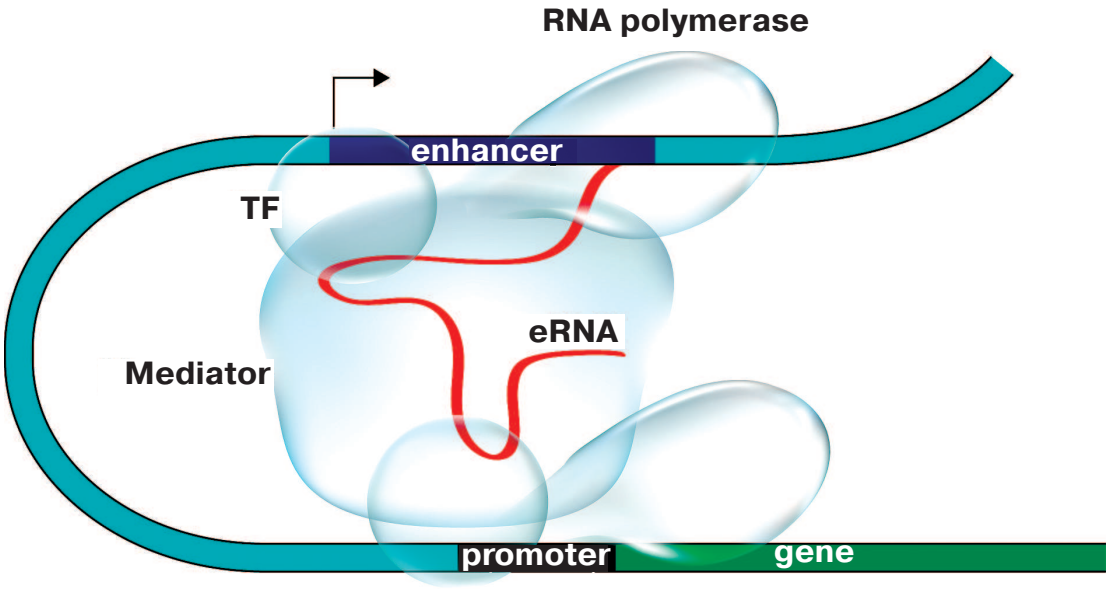

Fig. 3. Model of promoter–enhancer communication. Enhancer RNA (eRNA) plays the key role in establishing contacts between proteins bound to the enhancer and the promoter and facilitates the assembly of activator chromatin protein that triggers gene transcription. TF is the transcription factor.

The spatial genome organization on a larger scale can also be regulated with the involvement of noncoding RNA (as discussed in review [105]). It has been shown, for example, that the long noncoding RNA Firre is able to direct the colocalization of several genomic loci located on different chromosomes [106]. The XIST-RNA functioning under conditions of dosage compensation covers the entire X-chromosome, providing its heterochromatization and inactivation [107]. The noncoding RNA MALAT1 acts as a molecular "scaffold" for the assembly of speckles – the nuclear bodies containing components of the splicing apparatus, to which the active genes are attracted [105]. Currently, it is difficult to assess how common is the phenomenon of RNA involvement in the contacts of remote genomic elements and large-scale genome organization. This is a very young research field, and the available data concern the study of a rather limited set of noncoding RNAs and genomic loci.

Concluding remarks. The idea that the eukaryotic genome is arranged into loops of 50-150 kb is not new. A lot of evidence supporting the existence of such loops appeared as early as in the 1970s [108-111]. At that time it was believed that chromatin loops are fixed on some skeletal structure referred to as nuclear matrix, nuclear skeleton, or scaffold of metaphase chromosome [112]. Now it is clear that there is no such structure. It appears during the saline extraction of nuclei as a result of aggregation of different proteins, first of all, the proteins of RNP particles, in the interchromatin compartment [113]. At the same time, the procedure for obtaining nuclear matrix allows the fixation of particular elements of intranuclear organization, whereby the study of the nuclear matrix contributed to disclosing some principles of spatial organization of chromatin fibril in interphase chromosomes [113]. According to the nuclear matrix model, the DNA present within this structure must consist mainly of DNA fragments localized at the bases of chromatin loops [111]. It would be interesting to compare the properties of this DNA fraction with the currenly known data on the bases of topological DNA loops and inter-TADs. In a number of works, it has been demonstarted that the active genes and elongating complexes of RNA polymerase II are concentrated within the nuclear matrix-attached DNA [114-118]. This correlates well with the preferential localization of active genes in the inter-TADs [32, 43]. The nuclear matrix was shown to contain CTCF and the CTCF-dependent insulator from the domain of chicken β-globin genes [119, 120]. As it has been more than once mentioned above, the presence of CTCF-binding sites is typical of inter-TADs. The nuclear matrix-attached DNA was preferentially cleaved by DNA topoisomerase II [121, 122]. Currently, it was demonstrated that DNA topoisomerase II is colocalized with CTCF and cohesin at the TAD boundaries [123]. Finally, it has been reported that the inter-disks of polytene chromosomes of *Drosophila*, which coincide with inter-TADs [43, 124], are enriched in DNA sequences preferentially binding to the nuclear matrix [125]. All the above leads to a conclusion that the DNA fraction isolated within the nuclear matrix consists mainly of the marginal areas of TADs and, probably, contact domains of other levels. In light of this conclusion, it seems important to reconsider the entire array of experimental data on the spatial organization of eukaryotic DNA that were obtained in the last quarter of the 20th century and attempt to integrate these data into the moderm models of structural and functional organization of the eukaryotic genome.

With reference to the modern models, it is clear that they will also be improved and modified with the accumulation of new experimental data. Among the most topical current trends in the study of spatial genome organization, we should mention the transition from cell population to single cell studies [59]. The emergence of a wide range of so-called C techniques [126] has substantially extended our insight into the spatial organization of eukaryotic genomes. However, observations have been made so far mostly in cell population studies. Hence, the findings concern only the most probable chromatin configurations [59]. The question to what extent, e.g., TADs or A/B chromatin compartments are the result of averaging the panel of different configurations adopted in single cells needs further investigation.

It seems equally important to study chromatin fibril dynamics, inter alia, by different methods of *in vivo* visualization of individual genomic loci [127]. Dynamic organization is an important characteristic of biological systems. Continuous alternation of different chromatin configurations offers an opportunity for cell differentiation and adaptation to changing external conditions via temporary fixation of configurations required for the expression of various groups of genes [128]. The particular mechanisms underlying all these processes are yet to be elucidated in further studies.

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