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REVIEW

Nuclear Matrix and Structural and Functional Compartmentalization of the Eucaryotic Cell Nucleus

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Abstract—Becoming popular at the end of the 20th century, the concept of the nuclear matrix implies the existence of a nuclear skeleton that organizes functional elements in the cell nucleus. This review presents a critical analysis of the results obtained in the study of nuclear matrix in the light of current views on the organization of the cell nucleus. Numerous studies of nuclear matrix have failed to provide evidence of the existence of such a structure. Moreover, the existence of a filamentous structure that supports the nuclear compartmentalization appears to be unnecessary, since this function is performed by the folded genome itself.

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The one hundred year anniversary of the birth of Ilia Borisovich Zbarsky (1913-2007), one of pioneer researchers in the field of nuclear organization, was celebrated in 2013. Sixty-five years ago, in 1949, an article "On the proteins of the cell nuclei" by him and his coauthor, Prof. Debov, was published [1]. This work initiated a new concept of the nucleus and its architecture. Indeed, for many years biochemists and then molecular biologists considered the cell nucleus as a reactor (tube) inside which different biochemical processes providing genome functioning take place. It was generally accepted that different enzymes, including DNA- and RNA-polymerases, exist in soluble form, and, after binding to DNA, move along it to synthesize DNA or RNA. However, now the picture of the organization of functional processes in the cell nucleus seems rather more complex. It has been shown that quite complex structure and functional compartmentalization are characteristic for the eukaryotic nucleus [2-5]. According to their function, replication and transcription factories that contain working DNA- and RNA-polymerases are the most important compartments [6-8]. A particular case of the transcriptional factory is represented by a nucleolus, where RNA-polymerase I conducts the synthesis of ribosomal RNAs. Current views regarding functional compartmentalization of the cell nucleus were formed gradually with accumulation of corresponding information. Development of adequate new methods of research, such as various methods of immunofluorescence staining, confocal microscopy, and other microscopic methods, have played a significant role. The importance of the spatial organization of the genome and different processes of synthesis carried out with the participation of the genome in great degree promoted convergence of molecular and cell biology, and now these fields of research represent a practically unified research field. Works on study of so-called nuclear matrix that were started in the middle of the last century in the world and also in our country in Zbarsky's laboratory have played an important role in this process. We will consider in this review the results of nuclear matrix studies and consider the current state of knowledge in the field of the structural basis of nucleus compartmentalization in the cell.

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Initial works studying internal organization of the cell nucleus and discovery of nuclear matrix. It was shown in the middle of the last century by some researchers that the cell nucleus contains a network of filaments composed of RNA and proteins [9, 10]. Other authors showed that the nucleus retains its shape and certain morphological features even after extraction of most of the chromatin [11, 12]. These observations suggest that there is a structure inside the eukaryotic cell nucleus that supports the internal organization of the nucleus (possibly a network of filaments). This idea was finally formulated by Berezney and Coffey in 1974, who suggested naming this structure the nuclear matrix [13]. They suggested that the nuclear matrix has predominantly protein nature, because it is not degraded by treatment with DNases and RNases. Electron microscopic images presented in the above-cited work showed the presence of a nuclear lamina, residual nucleoli, and filamentous network in the nuclear matrix. This filamentous network was named internal or diffuse matrix [13]. Results obtained by Berezney and Coffey differed slightly from the results that have been obtained 10 years before in Zbarsky's laboratory, and, most likely, would stay unnoticed if the same authors did not demonstrate that newly synthesized DNA is preferentially attached to the nuclear matrix [14]. This observation lead to a long history of study of the nuclear matrix, which then was considered as a platform for assembly of various multienzyme complexes [8, 15-19]. After revealing different functional compartments inside the nucleus, the nuclear matrix came to be considered as a structural basis for compartmentalization [20, 21]. Indeed, practically all characterized nuclear compartments were revealed in preparations of isolated nuclear matrix after removal of the bulk of chromatin [20, 22-24]. It was demonstrated practically simultaneously with discovery of the nuclear matrix that after solubilization of histones, total nuclear DNA remained bound to residual proteinaceous structures (nuclear matrix), being organized into topologically closed loops with average size of 50-250 kb [25-27]. These findings suggested that the nuclear matrix plays an important role in folding of interphase chromosomes. Similar DNA loops were also revealed in metaphase chromosomes after extraction of histones [28]. This suggested that the organization of DNA into loops attached to chromosomal skeleton elements was preserved in the course of the full cell cycle [29]. It was also suggested that DNA loops attached to the nuclear matrix may represent some structural and functional units (domains) of the genome [30]. Taken in combination, these observations lead to the study of the nuclear matrix as it is (protein composition and ultrastructure) and specificity of DNA attachment to the nuclear matrix. These issues will be considered here in detail in the next sections.

Structure and protein composition of nuclear matrix. Berezney and Coffi declared in their initial publications that three proteins with molecular mass of approximately 70 kDa, which were identified as nuclear lamina proteins, were the main components of the nuclear matrix [13, 15]. Afterwards, it has been demonstrated that the protein composition of the nuclear matrix is more complex [31-33]. These contradictions were seemingly due to an instability of the internal (diffuse) nuclear matrix. During isolation of the nuclear matrix from various cells in accordance with the original protocol of Berezney and Coffey, this part of the nuclear matrix was completely or partly lost [34]. Incubation of nuclei in the presence of Cu^{2+} [34, 35] and other bivalent cations [36] and treatment with agents that promote formation of disulfide bonds (for example, by sodium tetrathionate) [34] stabilized the diffuse matrix. A similar result was obtained after incubation of nuclei at 37°C [37, 38]. In great degree, the diffuse matrix is composed of proteins of ribonucleoprotein (RNP) particles [39, 40]. Matrins [41, 42], actin [43, 44], NuMA [45-47], and DNA-topoisomerase II [48-52] represent other typical components of the diffuse matrix. In contrast to lamins, all the listed proteins are not exclusive components of the nuclear matrix. They are also present in extracted fractions. For many years the following question was debated – is the diffuse nuclear matrix constantly present in the living cell, or it is formed during chromatin solubilization as a result of protein aggregation? To answer this question, many researchers tried to characterize the filaments that constitute the diffuse nuclear matrix. The network of filaments can be seen in the nuclear matrix inspected under an electron microscope [53-55]. However, the nature of these filaments is still unclear. The most typical components of the isolated nuclear matrix do not form filamentous structures in the living cell (this issue is described in detail in a review by Hancock [56]). In some cases, actin and lamins are in filaments inside the nucleus of living cells, but these filaments do not form a unified network like the cytoskeleton and the network of filaments that are revealed in isolated nuclear matrix [57, 58]. Some nuclear matrix proteins, including proteins of RNP particles and NuMA, readily form filaments *in vitro* and *in vivo* under conditions of their overexpression in living cells [59-62]. This suggests that the internal matrix is formed *de novo* as a result of aggregation of proteins in the interchromatin compartment that might occur during extraction of nuclei with high-salt solutions [63]. We will return to discussion of this issue after a brief review of works that were directed to the study of the nuclear matrix DNA.

Nuclear matrix DNA. Demonstration of the fact that genomic DNA in interphase nuclei and metaphase chromosomes is organized in the form of loops attached at chromosomal skeletal elements (nuclear matrix or chromosomal skeleton) [25, 28, 64] insoluble in high-salt solutions stimulated studies on the specificity of DNA organization into loops. Two questions were considered in these works: (1) Are specific DNA sequences necessary

for DNA loop anchorage to the nuclear matrix? And (2), are individual DNA sequences arranged specifically or randomly in relation to sites of DNA attachment at the nuclear matrix? Clear answers for these questions have not been obtained. It was noted in the first studies that DNA sequences attached at the nuclear matrix are rich in repetitive elements [29, 65, 66]. However, no definite class of repetitive DNA sequences typical for DNA attached to the nuclear matrix was found [67]. Other authors reported that there was no difference between nuclear matrix-attached DNA and total DNA [68]. A critical attitude regarding the procedure of histone extraction with concentrated saline solution due to possible stimulation of protein aggregation motivated the development of new approaches for isolation of the nuclear skeleton. The best-known procedure is the extraction of nuclei by a weak ionic detergent – lithium diiodosalicylate [69]. Using this procedure, preparations of residual nuclear structures that contained specific genomic elements that were apparently involved in attaching DNA loops at the nuclear scaffold were obtained. These genomic elements were named scaffold attachment regions (SARs) [69-71]. Other authors have shown that there are particular classes of DNA sequences in eukaryotic genomes that *in vitro* specifically bind to the nuclear matrix in the presence of an excess of competitor prokaryotic DNA [72, 73]. These genome elements were named matrix association regions (MARs). Subsequent studies showed that there are no differences between MARs and SARs. Moreover, it was revealed that nuclear matrix (nuclear scaffold) preparations, isolated using lithium diiodosalicylate, can be used *in vitro* in experiments on isolation of MARs [74]. Currently, the term "S/MAR" is often used instead terms "MAR" or "SAR" [75]. S/MAR-elements do not share homologous nucleotide sequences, but they possess some common characteristics, including relative enrichment in A/T-pairs and the ability to be preferentially melted in supercoiled DNA [76, 77]. Properties of S/MAR-elements have been described in several reviews [67, 75, 78]. So, here we will not consider the properties of S/MAR-elements in detail. It should only be noted that they are not tissue- and species-specific elements [73]. It is also important that S/MAR-elements were found inside genes and even inside exons [79]. Despite the conviction of many researchers that the S/MAR-elements participate in attachment of DNA to the nuclear skeleton, there is no direct evidence for this. Moreover, it has been shown that S/MAR-elements can be removed from the nucleus by electroelution under physiological ionic strength [80], which weakly correlates with their postulated role in the attachment of DNA loops to the nuclear skeleton (matrix).

Using various methodological approaches, many proteins that preferentially bind to S/MAR-elements have been identified [81, 82]. Among them lamins [83], SATB-1 (special AT-rich sequence binding 1) [84, 85], and SAFA/hnRNP-U [40, 86] are the best known. Independently from the possible role of these proteins in attachment of DNA to the nuclear matrix, they may also play an important role in the maintenance of the architecture of interphase chromosomes. SATB-1 is more studied here, and it has been shown using a chromosome conformation capture method that it directly participates in supporting functionally important interactions between remote elements in the genome [87-90].

Works studying the specificity of chromosomal DNA organization into loops independently of the presence of specific genomic DNA at the base of the loops were started in Cook's laboratory [91] few years after the discovery of eukaryotic nucleoids (residual nuclei that contain DNA loops attached to the nuclear matrix [25, 92]) and continued in several other laboratories [93-96]. However, the results of these studies were rather surprising. It was found that actively transcribing genes localize at the base of loops or very close to them, while silent genes were mapped at distal parts of loops. The position of tissue-specific genes inside loops depended on the type of cell differentiation and could be altered in relation to their transcriptional status. For instance, the chicken ovalbumin gene becomes attached to the nuclear matrix during estrogen-stimulated differentiation of ovary cells [94]. In combination with the previously known fact of attachment of replicating DNA to the nuclear matrix [14, 97], all the results of the works cited above indicated that DNA organization as a loop is a dynamic process, and it directly reflects the functional activity of a genome [21]. However, some observations do not support this model [21]. In particular, it was shown that there are so-called permanent sites of DNA attachment to the nuclear matrix, and it was possible to detect them in inactive nuclei of chicken erythrocytes [98, 99] and sperm nuclei [100]. The fact of DNA organization as loops in inactive sperm nuclei [101-103] distinctly indicates that this organization exists independently of replication and transcription activity. We suggested that there are permanent (independent of replication and transcription) as well as functionally dependent sites of DNA attachment to the nuclear matrix [104]. To map permanent sites of DNA attachment to the nuclear matrix, a method of DNA loop excision by DNA-topoisomerase II of the nuclear matrix was developed [105-108]. Using this experimental procedure, maps of genomic DNA organization into loops for some segments of the genome of different organisms were constructed, including a map of the organization into loops of a human dystrophin gene [109]. It is most important that this map has been verified by hybridization with nuclear halos of bacmid probes that correspond to the mapped DNA loops. Thus, it was for the first time demonstrated that DNA loops mapped with the use of biochemical methods correspond to loops that can be observed in cytological preparations [109]. Investigation

of developmental changes of chromatin loop organization in *Xenopus laevis* showed increasing size of loops during ontogenesis and change in specificity of DNA attachment to the nuclear matrix [110-112].

Nuclear matrix in the context of cell nucleus compartmentalization. Demonstration of the fact that replication and transcription processes proceed at the nuclear matrix (skeleton) gave a great impulse to study of spatial organization of different processes in the cell nucleus, and this promoted understanding of the importance of functional compartmentalization in the cell nucleus. During a relatively short time period, replication [8, 113, 114] and transcription [115-117] factories, splicing "speckles" [118, 119], and many other functional compartments were discovered [2, 120, 121]. It seemed logical to assume that a platform should exist for assembling and positioning of functional compartments inside the nucleus. For many years nuclear matrix was considered as this platform [20, 24, 122]. Indeed, different researchers showed that practically all known nuclear compartments are preserved in isolated nuclear matrix after removal of most of the chromatin [20, 113, 123, 124]. At the same time, the nature of nuclear matrix was not yet revealed [57, 58]. Certain concern of researchers was caused by the contradiction between results that demonstrate preferential sensitivity of active genes to exogenous nucleases [125] and mediation of transcription at the nuclear matrix. Indeed, DNA sequences that are localized in the base of loops are less available for the action of nucleases [91]. This contradiction is readily explained using the suggestion that diffuse (internal) nuclear matrix is formed as a result of protein aggregation during chromatin extraction. In this connection, it is appropriate to remember that there are chromosomal territories and so-called interchromatin domain in the nucleus [126-128]. First, it was considered that this domain localizes predominantly between chromosomal territories [128]. However, it was then demonstrated that a network of interchromatin channels spans chromosomal territories [126, 129, 130], making their internal areas available for different proteins, including exogenous nucleases. Replication and transcription factories are located at the surface of interchromatin channels that are used also for transport of RNA to the cytoplasm [63]. It looks very probable that, in the course of nuclear matrix isolation, proteins of RNP particles present inside interchromatin channels aggregate with formation of a network of filaments, which was named internal or diffuse matrix [60, 63]. Attracting forces that arise under conditions of macromolecular crowding may promote this process [56]. Taking into account all the above-mentioned data, it is possible to state that the diffuse nuclear matrix (i.e. an irregular network of fibrils and granules) is undoubtedly an artifact structure. At the same time, formation of this structure during chromatin solubilization preserves the initial positioning of nuclear compartments in the absence of chromatin. In this connection, a procedure of nuclear matrix isolation can be considered as a fixation method that allows making observations that are impossible to make using nuclei fixed by other methods. For example, it is appropriate to note that ovoid structures representing replication factories were discovered during studies of nuclear matrix (nuclear skeleton) preparations by electron microscopy [113].

Folded genome as a platform for functional compartmentalization of the cell nucleus. If the nuclear matrix does not exist as a unified filamentous structure, then what serves as a platform for functional compartmentalization of the nucleus? There is solid basis to suggest that this platform is provided by genomic DNA itself folded into chromatin [13-133]. In this connection, most important is the fact that the chromatin fibril constituting an interphase chromosome is organized in the nucleus in a rather complex manner. It is appropriate to mention the functional architecture of interphase chromosomes that is supported by a system of interactions between remote genomic elements. Existence of such interactions inside chromosomes as well as between different chromosomes was shown in a number of works carried out with the use of a chromosome conformation capture (3C) procedure [134] and derived full-genome C-methods [135-140]. Territorial organization of interphase chromosomes provides the existence of an interchromatin domain that contains many nuclear compartments, including SC35 speckles (splicing "speckles"), PML bodies, and Cajal bodies [127, 128, 130, 141]. Other compartments, such as transcription factories (including also a nucleolus) and replication factories, are formed with direct participation of DNA. According to one point of view, assembly of different groups of genes into transcription factories is one of the most important determinants supporting the architecture of interphase chromosomes [142, 143]. An alternative point of view according to which transcription factories contain genes that for any reason are close to each other in the cell nucleus space deserves equal attention [144]. As for replication factories, they may represent basic structural blocks of a chromosome [145] that are revealed as topologically associated domains (TADs) by the Hi-C method [135]. It has been known for a long time that different types of heterochromatin domains are concentrated near the nuclear lamina and in nucleolus adjacent layer (chromatin domains known as LADs [146, 147] and NADs [135, 140, 148]) or combined into so-called Polycomb-bodies [149-153]. Assembly of inactive chromatin domains proceeds with involvement of HP1 and H3K9 histone methylase or with the participation of Polycomb proteins. Various structures of higher order in the chromatin are relatively labile. Structural components of heterochromatin demonstrate relatively high rates of exchange [154-156]. In other words, the existing heterochromatin domains represent a product of dynamic equilibrium between processes of assembly and disassem-

bly. Spatial association of such domains in a lamina adjacent layer or in Polycomb-bodies must shift the equilibrium toward assembly due to high local concentration of heterochromatin proteins and enzymes that catalyze modification of histones necessary for heterochromatin formation. Attraction of any genes to such areas, for example, the lamina adjacent layer, will lead to their inactivation due to high local concentration of factors that promote inactive chromatin formation [157-160].

For many years, the concept of nuclear matrix remained attractive despite the quite well-founded criticism because it suggested an explanation of what the structural basis for the functional compartmentalization of a cell nucleus is [161]. Realization of the fact that the interphase chromosome organized in space due to interaction between remote genomic elements stabilized by architectural proteins [162-165] is itself a platform for the cell nucleus compartmentalization makes the concept of the nuclear matrix completely unnecessary.

The concept of nuclear matrix as a skeletal basis of the cell nucleus has now been fully exhausted. Numerous studies attempting to characterize the nature of the nuclear matrix failed to provide evidence for the existence of such a structure. According to a logical point of view, the existence of a filamentous structure that supports the nuclear compartmentalization is unnecessary, because this function is performed just by the genome folded in a complex manner in the nuclear space. Moreover, it would be very difficult to explain the dynamic character of the nuclear compartmentalization in the frame of the concept of the nuclear matrix [166-170]. All the above-said does not mean that there are no skeletal elements in the nucleus. There is much evidence in the scientific literature that various non-coding RNAs have skeletal functions during assembly of different nuclear compartments [171-174]. It can be anticipated that the number of characterized RNAs that perform skeletal functions will significantly increase. However, there are no grounds to state that non-coding RNA form a unified nuclear skeleton. All works mentioned above concerned solving of local tasks. It is necessary to remember that there are other compounds, for example phospholipids, in the cell nucleus in addition to nucleic acids and proteins. Some observations suggest that sphingomyelin plays a certain role in the organization of the intranuclear space [175-179]. These results are simply ignored by the majority of researchers who study the cell nucleus compartmentalization. In this connection, it is necessary to note that the existence of DNA was similarly ignored until the middle of the last century.

It is not possible to explain all the observations made during studies of the nuclear matrix only by RNP particle aggregation in interchromatin channels in the course of histone extraction by high-salt solutions. It was shown that DNA is organized as loops in inactive nuclei of avian erythrocytes and in mammalian and avian sperm cells (where no RNP particles are formed) [180-183], and these loops are similar to those revealed in active nuclei. It is logical to assume that certain architectural elements that keep the ends of these loops together should exist. Having no intention to reanimate the concept of nuclear matrix, we nevertheless believe that it is important to say that the question of the existence of different architectural elements in the cell nucleus that maintain intranuclear organization at local levels needs further clarification.

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