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REVIEW

A requiem to the nuclear matrix: from a controversial concept to 3D organization of the nucleus

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Abstract The first papers coining the term "nuclear matrix" were published 40 years ago. Here, we review the data obtained during the nuclear matrix studies and discuss the contribution of this controversial concept to our current understanding of nuclear architecture and three-dimensional organization of genome.

Introduction and brief history

Forty years ago, Berezney and Coffey published a paper entitled "Identification of a nuclear protein matrix" (Berezney and Coffey, 1974). The paper described the isolation of a proteinaceous residual nuclear structure that retained the shape and some morphological features of a cell nucleus after removal of chromatin. Similar residual nuclear structures had been observed previously by several authors (e.g.. Georgiev and Chentsov, 1963; Narayan et al., 1967; Zbarsky and Debov, 1949), but these observations did not draw much attention of the researchers. The article published by Berezney and Coffey would have also remained unnoticed if the same authors have not published a second "nuclear matrix" paper demonstrating association of newly replicated DNA with the nuclear matrix (Berezney and Coffey, 1975). This functional link ensured the success and the long life of the nuclear matrix concept. The discovery of the structural platform for the organization of synthetic processes within the cell nucleus had long been anticipated. Active replication origins are associated with cellular membrane in prokaryotic cells (Fielding and Fox, 1970; Sueoka and Quinn, 1968). The attempts to demonstrate a similar association in eukaryotic cells produced controversial results. Although some authors reported association of replicating DNA with the nuclear membrane (e.g., Infante et al., 1976; O'Brien et al., 1972), the detergent treatment-based methods they used in these studies for isolation of membrane-bound DNA led to isolation of DNA bound to nuclear lamina or other proteinaceous strictures rather than to membrane composed of lipids soluble in the detergents used. Hence, the introduction of proteinaceous nuclear matrix as a structural platform for organization of replication machinery in eukaryotic cells was met with enthusiasm. Subsequent demonstration of preferential association of active genes and transcription machinery with the nuclear matrix (Jackson et al., 1981; Jost and Seldran, 1984; Razin et al., 1985; Robinson et al., 1982) led to consideration of the nuclear matrix as a universal platform for spatial organization of both replication and transcription (reviewed in Berezney et al., 1995; Jackson and Cook, 1995).

In the following years, the studies of the nuclear matrix were concentrated on three directions:

1. Ultrastructure and protein composition of the nuclear matrix
2. Visualization of the nuclear matrix in fixed and living cells
3. Characterization of DNA sequences attached to the nuclear matrix

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All three lines of studies resulted in controversial findings and conclusions. Still the idea that a structural platform was necessary to support the spatial organization of replication, transcription, and other functional processes occurring in the cell nucleus turned out to be so attractive that the concept of the nuclear matrix survived over the last 40 years, although the existence of the nuclear matrix was questioned by many scientists during all this time. The key results obtained in studies of the nuclear matrix in relation to current models of functional compartmentalization of eukaryotic cell nucleus will be discussed below.

Ultrastructure and protein composition of the nuclear matrix

Inspection of the isolated nuclear matrix under electron microscope revealed an internal network of irregular fibers associated with granules of various sizes (Berezney and Coffey, 1977). This irregular network appeared to be composed of underlying 10-nm core filaments of unidentified nature (Nickerson, 2001). They were reported to consist of proteins with characteristics of intermediate filaments (Jackson and Cook, 1988). Different authors reported the presence of actin (Amankwah and De Boni, 1994), lamins (Hozak et al., 1995), nuclear mitotic apparatus (NuMA) (Zeng et al., 1994), and proteins of nuclear ribonucleoproteins (RNP) particles (He et al., 1991; Mattern et al., 1996; Mattern et al., 1997) in the nuclear matrix filaments. However, none of these proteins appeared to be present in all nuclear matrix filaments. Furthermore, some of these findings were not confirmed by independent studies (for a review see Jack and Eggert, 1992; Nickerson et al., 1989).

The nuclear protein matrix was initially reported to be composed for the most part of nuclear lamins (Berezney and Coffey, 1974; Berezney and Coffey, 1977). Subsequent studies demonstrated that the protein composition of the nuclear matrix is much more complex (Berezney, 1980; Long et al., 1979; Verheijen et al., 1988), yet only lamins appeared reproducibly in the nuclear matrix preparations (Lebkowski and Laemmli, 1982). Other non-histone proteins can be found both in soluble and insoluble fractions in the nuclear matrix preparations. Besides the above mentioned actin, NuMA and proteins of RNP particles, proteins typically present in the nuclear matrix include matrins (Nakayasu and Berezney, 1991; Zeitz et al., 2009), DNA topoisomerase II (Berrios et al., 1985; Feister et al., 2000 2768; Kaufmann and Shaper, 1991; Valkov et al., 1997; Vassetzky et al., 2000) and a range of other proteins (Mika and Rost, 2005), reviewed in (Albrethsen et al., 2009).

Importantly, the protein composition of the nuclear matrix was found to vary significantly depending on subtle changes in the isolation procedure. In particular, the presence of oxidative agents and Cu^{2+} or C^{a2+} ions in the course of the nuclear matrix preparation were reported to drastically enrich the protein composition of the nuclear matrix (Kaufmann et al., 1981; Lebkowski and Laemmli, 1982; Lewis et al., 1984; Rzeszowska-Wolny et al., 1988). Similar effect could be obtained by isolation of the nuclear matrix in the presence of divalent cations (Neri et al., 1999) or by heating at 37 °C (Martelli et al., 1991; Martelli et al., 1995). Careful consideration of the effects of different variations in the nuclear matrix preparation procedure on protein composition and ultrastructure of the isolated nuclear matrix made it possible to conclude that the so-called internal nuclear matrix is rather unstable and is not preserved under certain conditions of nuclei fractionation (Kaufmann et al., 1981; Lebkowski and Laemmli, 1982). By varying the order of extraction steps and the extent of disulfide cross-linking, it was possible to isolate from a single batch of nuclei residual structures with a wide range of morphologies and compositions, from empty nuclear shells to nuclear matrixes possessing an extensive internal network (diffuse matrices) (Kaufmann et al., 1981; Lewis et al., 1984). These observations can be explained both by the supposition that the internal nuclear matrix is unstable (thus stabilization is necessary to isolate it) and by the supposition that the internal nuclear matrix does not exist in living cells and is formed by aggregation of proteins under certain experimental conditions. The existing experimental evidence does not permit to make a choice between the above options. We shall return to this problem later.

Visualization of the nuclear matrix in fixed and living cells

To find out whether the nuclear matrix exists in non-fractionated cell, many scientists attempted to visualize filamentous structures in the nuclei of fixed or living cells. These attempts also produced controversial results. The majority of proteins isolated from the nuclear matrix could not be observed as fibrillar structures after immunostaining of fixed cells (for a review see Hancock, 2000). Although filaments composed of actin and lamins were occasionally observed within non-extracted nuclei, they did not form a network similar to isolated nuclear matrix (for a review see Pederson, 1998, 2000). Several other proteins reported to be components of nuclear matrix were observed as fibers or lattices of different structure in both fixed and living cells (Barboro et al., 2002; Barboro et al., 2003; Gerner et al., 1999; Gueth-Hallonet et al., 1998; Menz et al., 1996). However, the relation of these structures to the filaments of isolated nuclear matrix remained obscure. It is of note that some of nuclear matrix proteins (hnRNP proteins, NuMA) readily form filamentous structures in vitro and in vivo upon overexpression in living cell (Gueth-Hallonet et al., 1998; Saredi et al., 1996; Tan et al., 2000). The proteins extracted from the nuclear matrix readily reassemble into a filamentous structure (Vassetzky et al., 1994). It is thus tempting to suggest that similar structures may be formed de novo during preparation of nuclear

matrices. Aggregation of different proteins in the course of nuclear matrix isolation may be promoted by high concentration of these proteins within interchromatin channels (see below and Razin and Gromova, 1995).

So far, there is no conclusive evidence for the existence of a rigid proteinaceous nuclear matrix inside the eukaryotic cell nucleus. On the other hand, there is a possibility that dynamic associations of various proteins supported by different forces including molecular crowding (Hancock, 2000, 2004, 2014) may fulfill most of the functions originally attributed to the nuclear matrix.

Characterization of DNA sequences attached to the nuclear matrix

Soon after the publication of the first "nuclear matrix" paper (Berezney and Coffey, 1974), it was reported that nuclear DNA was associated with high-salt-insoluble nuclear remnants that resembled the nuclear matrix (Cook et al., 1976). It appeared that DNA was organized into constrained loops periodically attached to the nuclear matrix (Cook and Brazell, 1976). Later, large DNA loops attached to proteinaceous nuclear matrix or scaffold of metaphase chromosomes were visualized by electron microscopy (Hancock, 1982; Paulson and Laemmli, 1977). The most interesting feature of these DNA loops was, perhaps, their size (50–200 Kb according to different estimations (Berezney and Buchholtz, 1981; Buongiorno-Nardelli et al., 1982; Hartwig, 1982; Lebkowski and Laemmli, 1982; Mullenders et al., 1983; Vogelstein et al., 1980), reviewed in (Razin, 1996; Razin and Gromova, 1995). At this size, range one could expect to find correlations between functional and structural organization of the genome predicted by the domain model of eukaryotic genome organization (Bodnar, 1988). This stimulated numerous studies on the nature of DNA sequences located at the bases of DNA loops and on the specificity of DNA organization into loops. As usual, in the studies of the nuclear matrix, controversial results were reported. Despite the initial enthusiasm provoked by demonstration of the enrichment of nuclear matrix DNA in repetitive sequences (Razin et al., 1978, 1979), no specific DNA sequence element responsible for the high salt-resistant association of DNA with the nuclear matrix were identified (reviewed in Boulikas, 1993; Razin, 1996; Razin and Gromova, 1995). Studies of the specificity of DNA organization into loops demonstrated that all DNA sequences currently involved in replication and transcription were preferentially associated with the nuclear matrix (Cook and Brazell, 1980; Cook et al., 1982; Jackson and Cook, 1985; Robinson et al., 1983; Small et al., 1985); reviewed in Razin, 1996; Razin and Gromova, 1995). It thus appeared that all interactions of DNA with the nuclear matrix were dynamic and functionally dependent (Jackson and Cook, 1995). This model was questioned by identification of so-called permanent sites of DNA attachment to the nuclear matrix that retain their integrity in non-active nuclei of avian erythrocytes (Razin et al., 1986; Razin et al., 1985). Later, it was found that the same sites can be mapped as located at the bases of DNA loops by topoisomerase II-mediated DNA loop excision procedure (Gromova et al., 1995; Lagarkova et al., 1998; Razin et al., 1993; Razin et al., 1991). Most important, it was demonstrated that an individual DNA loop mapped by this biochemical approach can be visualized by in situ hybridization of the appropriate BAC probe with the so-called nuclear halos (Iarovaia et al., 2004) and thus corresponded to DNA loops that had been initially described by Cook and Brazell (Cook et al., 1976). Of course, this does not mean that partitioning of the genomic DNA into loops is entirely static. Association of replicating DNA with the nuclear matrix initially was reported by Berezney and Coffey (Berezney and Coffey, 1975) and confirmed by other authors (Hunt and Vogelstein, 1981; McCready et al., 1980; Vaughn et al., 1990). If indeed DNA polymerase is fixed in some way (perhaps, just by stochastic association of several replication forks into a replication factory (Saner et al., 2013), DNA should be pulled through this complex. This movement was indeed observed in one recent study (Kitamura et al., 2006).

An attractive biochemical technique to map association of DNA with the nuclear matrix was developed in the 1980s. It allows to monitor the ability of specific DNA fragments to bind in vitro nuclear matrices isolated either using high-salt extraction (Cockerill and Garrard, 1986b) or a chaotropic agent lithium diiodosalicylate (LIS) (Gasser and Laemmli, 1986a, b; Mirkovitch et al., 1984). The high-salt extraction method allowed to identify mostly AT-rich sequences that were neither tissue nor species-specific (Cockerill and Garrard, 1986a), while LIS extraction revealed different subsets of similarly AT-rich sequences in different cell lineages (Gasser and Laemmli, 1986a). These sequences were termed as nuclear scaffold (or matrix) attachment regions (S/MARs). S/MARs are quite ubiquitous in the genome and generally are located at distances that are smaller than the size of DNA loops (Brun et al., 1990). They interact with DNA topoisomerase II molecules (Eivazova et al., 2009; Gasser and Laemmli, 1986a) and some specific proteins, including special AT-binding protein (SATB1) (Nakagomi et al., 1994). A comparison between the in vitro S/MARs and the DNA loops revealed that only a small part of S/MARs serve as loop bases in somatic cells (Iarovaia et al., 1996). In agreement with these observations, it was shown that some bona fide SARs could be electroeluted from nuclei in "physiological conditions" and thus are not attached to any internal nuclear structure (Hempel and Stratling, 1996).

Summarizing one may conclude that partitioning of genomic DNA into large topological loops is specific although the sequences located at the bases of DNA loops cannot be described by any simple consensus and do not belong to any

specific class of repetitive elements. Earlier observations suggest that origins of DNA replication are located at the bases of such loops (Amati and Gasser, 1988; Lagarkova et al., 1998; Razin et al., 1986). Large DNA loops can be temporarily subdivided into smaller units due to association of transcribing and replicating DNA sequences with the nuclear matrix (Lemaitre et al., 2005; Razin, 1987; Vassetzky et al., 2000).

Interchromatin channels and artificial formation of internal nuclear matrix filaments during extraction procedures

There is a clear contradiction between the well-established sensitivity of active genes to exogenous nucleases (Weintraub and Groudine, 1976) and the reported association of active genes with the nuclear matrix (see the "Characterization of DNA sequences attached to the nuclear matrix" section). Indeed, according to the mapping procedure, DNA sequences attached to the nuclear matrix were expected to be relatively resistant to nucleases used to cut off the DNA loops (Cook and Brazell, 1980). To solve this apparent contradiction, we proposed the channel model of the nuclear matrix (Razin and Gromova, 1995). The nuclear matrix was considered as a system of channels spanning chromosomal territories and used for transport of RNA (actually, RNP) from the places of synthesis toward the nuclear pores and transport of different compounds from cytoplasm to the places of their utilization within the cell nucleus. The transcription and replication factories (and thus transcribing and replicating DNA sequences) were postulated to reside at the surface of the channels. As long as channels existed, the exogenous nuclease could penetrate them and preferentially attack transcribing and replicating DNA sequences. This appeared to happen in permeabilized cells (Gromova et al., 1995). The key suggestion was that extractions and enzymatic treatments used to prepare the nuclear matrix resulted in a precipitation of nuclear proteins, a collapse of the channels and aggregation of proteins present in the channels (mostly hnRNP proteins). That is how the filaments of the internal nuclear matrix could be created (Razin and Gromova, 1995). Although formed artificially, the system of nuclear matrix filaments reflected the path of the channels and appeared to support positions of residual nuclear compartments seen in the nuclear matrix (Berezney et al., 1995). Even residual chromosomal territories occupied distinct non-overlapping positions in the isolated nuclear matrices after removal of the major portion of DNA (Ma et al., 1999). For this reason, the procedure of nuclear matrix (nuclear scaffold, nuclear skeleton, etc) isolation can be considered as a kind of fixation that allows for the analysis of functional nuclear compartments after chromatin removal. This approach turned out to be quite productive. For example, isolation of chromatin-depleted nuclear skeleton allowed for observation of morphologically discrete ovoid replication factories under the electron microscope (Hozak et al., 1993). It should be noted that the nature of the nuclear matrix channels (i.e., the forces that keep these channel free or relatively free of chromatin) remains obscure, although the existence of A-type lamin channels interacting with several nuclear components was recently reported (Legartova et al., 2013).

At the time the channel model of the nuclear matrix was proposed, the interchromatin compartment model already existed. According to the initial supposition (Cremer et al., 1993), the interchromatin compartment separated chromosomal territories and was maintained due to the electrostatic repulsion of chromatin masses. When it was shown that chromosome territories had a sponge-like structure (i.e., are spanned by interchromatin channels) (Cremer et al., 2001; Cremer and Cremer, 2010; Visser et al., 2000), both models became very similar. Unfortunately, it is still not clear what prevents the interchromatin channels from collapsing in living cells.

Is a filamentous structural platform (nuclear matrix) essential to support nuclear compartmentalization?

Most of the arguments in favor of the nuclear matrix are based on a supposition that a skeletal network should underlie the nuclear compartmentalization. However, the necessity of the special skeletal network within the eukaryotic cell nucleus was questioned by a supposition that folded chromatin itself can constitute a structural milieu for organization and positioning of functional compartments present in eukaryotic cell nuclei (Cremer et al., 1993; Marshall et al., 1997; Razin et al., 2013). In this regard, it is of note that the most important nuclear compartments (nucleolus, replication and transcription factories, Polycomb bodies) include DNA. Specific chromosomal regions (transcribed or repressed genes, replication forks, and DNA repair foci arranged in clusters) constitute nucleation centers for the assembly of all these compartments. Positions of all these genomic elements are constrained due to the specific folding of interphase chromatin, including organization of interphase chromosomes in topologically associated domains (TADs) (for review see Bickmore, 2013; Dostie and Bickmore, 2012). Mutual positions of different segments of interphase chromosome are stabilized by links mediated by architectural proteins, such as cohesin and CTCF (Ohlsson et al., 2010; Phillips-Cremins et al., 2013; Politz et al., 2013; Sofueva and Hadjur, 2012; Sofueva et al., 2013). Association of a set of chromosomal domains with the nuclear lamina further stabilizes the architecture of interphase chromosomes (Guelen et al., 2008; Meister and Taddei, 2013). This stabilization also involves long non-coding RNAs interacting with the tentative nuclear matrix proteins (Hacisuleyman et al., 2014). Of course, the 3D organization of interphase chromosomes is highly dynamic (Cavalli and Misteli, 2013; Dion and Gasser, 2013; Kind et al., 2013; Levi et al., 2005; Marshall, 2002; Marshall et al., 1997; Nagano et al., 2013; Pliss et al.,

2013), but so are the nuclear compartments. They are constantly assembled and disassembled around the genomic nucleation centers. The recent study of transcription factory dynamics provides a good example (Cisse et al., 2013). Nuclear bodies that do not include DNA (splicing speckles, PML bodies, Cajal bodies) may also be positioned by folding of a chromatin fiber because the place for the location of these nuclear bodies, the interchromatin compartment, is generated through a special mode of interphase chromosome folding (for more extensive discussion see Razin et al., 2013). All the above considerations question the functional necessity of nuclear matrix as a platform for nuclear compartmentalization.

Concluding remarks

Although the nuclear matrix was and remains a controversial concept, it paved the way to our current understanding of nuclear architecture. Further studies on 3D organization of the nucleus will provide rational explanation for the role of S/MARs and loop domains observed in the nuclear matrix studies in the dynamic organization of the nucleus.

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