ISSN 0006-2979, Biochemistry (Moscow), 2018, Vol. 83, No. 4, pp. 299-301. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © S. V. Razin, 2018, published in Biokhimiya, 2018, Vol. 83, No. 4, pp. 437-439.

Structural-Functional Organization of the Eukaryotic Cell Nucleus and Transcription Regulation: Introduction to This Special Issue of *Biochemistry* (*Moscow*)

S. V. Razin[1,2]

[1]*Institute of Gene Biology, Russian Academy of Sciences, 119334 Moscow, Russia*
[2]*Lomonosov Moscow State University, Biological Faculty, 119991 Moscow, Russia; E-mail: sergey.v.razin@usa.net*

Received January 9, 2018

Abstract—This issue of *Biochemistry* (*Moscow*) is devoted to the cell nucleus and mechanisms of transcription regulation. Over the years, biochemical processes in the cell nucleus have been studied in isolation, outside the context of their spatial organization. Now it is clear that segregation of functional processes within a compartmentalized cell nucleus is very important for the implementation of basic genetic processes. The functional compartmentalization of the cell nucleus is closely related to the spatial organization of the genome, which in turn plays a key role in the operation of epigenetic mechanisms. In this issue of *Biochemistry* (*Moscow*), we present a selection of review articles covering the functional architecture of the eukaryotic cell nucleus, the mechanisms of genome folding, the role of stochastic processes in establishing 3D architecture of the genome, and the impact of genome spatial organization on transcription regulation.

DOI: 10.1134/S0006297918040016

Keywords: chromatin, cell nucleus, spatial organization of the genome, macromolecular crowding, functional compartmentalization of the cell nucleus, 3D genomics, regulation of transcription

The idea to make an issue of *Biochemistry* (*Moscow*) dedicated to the cell nucleus and mechanisms of transcription regulation arose in connection with the holding in Russia of the 25th W. Bernhard International Conference on the Cell Nucleus (Nizhny Novgorod, June 19-22, 2017). The first such conference was organized by Wilhelm Bernhard in 1968. The major goal of that conference and of the subsequent ones of this series was to join researchers of various specialties, especially in cell and molecular biology, to solve the most important problems of experimental biology.

Over the years, biochemical processes in the cell nucleus were studied in isolation, outside the context of their spatial organization. The cell nucleus was considered a kind of container where various macromolecules were placed. Today it is clear that functional processes in the cell nucleus are spatially segregated. The structural and functional compartmentalization of the cell nucleus plays an extremely important role in the regulation of the eukaryotic genome functioning. The compartmentalization of the cell nucleus is closely related to the spatial organization of the genome that in turn is crucial for operation of epigenetic mechanisms [1]. It is important that the organization of the cell nucleus is dynamic. The assembly of functional compartments of the cell nucleus is guided by weak interactions that are stabilized by entropic forces arising under conditions of the macromolecular crowding. When the initial conditions change, these compartments are easily disassembled. As to the spatial organization of the genome, various configurations of interphase chromosomes are continuously revised in the nucleus, and this makes possible a short-term fixation of configurations corresponding to the current requirements of the cell.

This special issue of *Biochemistry* (*Moscow*) offered to the scientific community presents review articles that reflect the main trends in studies on the structural and functional organization of the cell nucleus. In this introductory article, I want to mention these trends and point out the key results that laid the foundation for modern concepts about the structural and functional organization of the cell nucleus and its importance for regulation of the genome activities. First, I would like to mention the works of Thomas Cremer et al. who discovered chromosomal territories and the interchromatin domain [2]. The works of these authors greatly contributed to the refutation of the nuclear matrix model and to the comprehension that the packed genome itself was a platform under-

lying the structural and functional compartmentalization of the nucleus. In the review article presented in this issue of the journal, T. Cremer et al. discuss the refined model of the structural–functional compartmentalization of the cell nucleus based mainly on their own results obtained by high-resolution microscopy [3]. The research of Thom Misteli demonstrating a high rate of the component exchange between the nuclear compartments and nucleoplasm is an important landmark in the study of organization of the cell nucleus that directly indicates the dynamic character of nuclear compartments [4]. Functional compartments of the nucleus, such as the nucleolus, Cajal bodies, PML-bodies, splicing speckles, and transcription factories are not surrounded with membranes. They are aggregates of proteins and, in some cases, of nucleic acids. Components of these compartments are held together due to relatively weak interactions with each other or with a certain component (protein or RNA) that is a structural platform for assembly of the compartment [5]. Under normal conditions, these weak interactions obviously would be insufficient for maintaining the integrity of a compartment. However, the entropic forces arising under the macromolecular crowding conditions typical for the karyoplasm significantly stabilize various macromolecular aggregates [6]. The role of entropic forces for establishing and maintaining the structural and functional organization of the nucleus and spatial organization of the genome is considered in detail in the review article by R. Hancock presented in this issue [7].

Spectra of active genes greatly depend on the repositioning of genomic domains between the active and repressive zones of the nucleus. In most eukaryotic organisms, the repressive zone of the nucleus is close to the lamina layer. A simple replacement of the gene into this region of the nucleus frequently results in its inactivation. Questions related to the role of the nuclear lamina in the spatial organization of the genome and the segregation of the active and inactive chromatin are considered in the review articles by Shevelyov and Ulianov [8] and by Sharakhov et al. [9].

The role of the genome spatial organization in the regulation of gene expression has been long known. However, until the beginning of this century, mainly the chromatin domain reconfiguration manifested by changes in their transcriptional status and accessibility for DNase I was discussed. The technique of chromosome conformation capture (3C) and derived experimental procedures [10] demonstrated that the physical distances between the genomic elements within the cell nucleus could be significantly different from the distances on the linear DNA molecule. Direct contacts between the remote regulatory elements are established on the level of the genome folding in 3D space, which play an important and perhaps the key role in the regulation of transcription [11]. The comprehension of this fact led to the emergence of 3D genomics, which can be used to explain many earlier unclear phenomena [12]. Questions concerning the role of the genome spatial organization in the regulation of transcription are considered in the review articles by Razin and Gavrilov [13], Kolesnikova [14], Tchurikov et al. [15], and Fishman et al. [16]. In the context of 3D genomics, it is possible to give a completely new explanation of the biological role of apparently senseless regions of the nucleotide sequence. These regions of the genome do not encode any protein; nevertheless, they can essentially influence the transcription of various genes by modulating the way of spatial packing of extended regions of the genome. It remains to elucidate the specific mechanisms of this influence. However, we think it necessary to show the readers what is known now about the repeating sequences of the eukaryotic genome. The review article by Podgornaya et al. [17] presents the corresponding material.

This issue also contains some other review articles analyzing specific problems related to the work of the eukaryotic genome [18-21].

A special place belongs to the article by E. D. Sverdlov [22] demonstrating the existence of fundamental prohibitions in biology. The existence of such prohibitions (problems lacking an unambiguous solution) is a consequence of the stochastic nature of most biological processes. The comprehension of this fact is extremely important for development of a reasonable strategy for studies in all areas of experimental biology.

Acknowledgments

This work was supported by the Russian Science Foundation (grant No. 14-24-00022).

REFERENCES

1. Razin, S. V., Gavrilov, A. A., Ioudinkova, E. S., and Iarovaia, O. V. (2013) Communication of genome regulatory elements in a folded chromosome, *FEBS Lett.*, **587**, 1840-1847.
2. Cremer, T., Kurz, A., Zirbel, R., Dietzel, S., Rinke, B., Schrock, E., Speicher, M. R., Mathieu, U., Jauch, A., Emmerich, P., Scherthan, H., Ried, T., Cremer, C., and Lichter, P. (1993) Role of chromosome territories in the functional compartmentalization of the cell nucleus, *Cold Spring Harb. Symp. Quant. Biol.*, **58**, 777-792.
3. Cremer, T., Cremer, M., and Cremer, C. (2018) 4D nucleome: genome compartmentalization in evolutionary context, *Biochemistry* (Moscow), **83**, 313-325.
4. Misteli, T. (2001) Protein dynamics: implications for nuclear architecture and gene expression, *Science*, **291**, 843-847.
5. Sleeman, J. E., and Trinkle-Mulcahy, L. (2014) Nuclear bodies: new insights into assembly/dynamics and disease relevance, *Curr. Opin. Cell Biol.*, **28**, 76-83.
6. Hancock, R. (2004) A role for macromolecular crowding

effects in the assembly and function of compartments in the nucleus, *J. Struct. Biol.*, **146**, 281-290.
7. Hancock, R. (2018) Crowding, entropic forces, and confinement: crucial factors for structures and functions in the cell nucleus, *Biochemistry* (Moscow), **83**, 326-337.
8. Shevelyov, Y. Y., and Ulianov, S. V. (2018) Role of nuclear lamina in gene repression and in maintenance of chromosome architecture in the nucleus, *Biochemistry* (Moscow), **83**, 359-369.
9. Sharakhov, I. V., Bondarenko, S. M., Artemov, G. N., and Onufriev, A. V. (2018) Role of chromosome–nuclear envelope attachments in 3D genome, *Biochemistry* (Moscow), **83**, 350-358.
10. De Wit, E., and De Laat, W. (2012) A decade of 3C technologies: insights into nuclear organization, *Genes Dev.*, **26**, 11-24.
11. De Laat, W., and Grosveld, F. (2003) Spatial organization of gene expression: the active chromatin hub, *Chromosome Res.*, **11**, 447-459.
12. Razin, S. V., and Vassetzky, Y. S. (2017) 3D genomics imposes evolution of the domain model of eukaryotic genome organization, *Chromosoma*, **126**, 59-69.
13. Razin, S. V., and Gavrilov, A. A. (2018) Structural–functional domains of the eukaryotic genome, *Biochemistry* (Moscow), **83**, 302-312.
14. Kolesnikova, T. D. (2018) Banding pattern of polytene chromosomes as a reflection of the universal principles of chromatin organization into topological domains, *Biochemistry* (Moscow), **83**, 338-349.
15. Tchurikov, N. A., Kravatsky, Y. V., and Kretova, O. V. (2018) Link between hot spots of DSBs and mechanisms of transcriptional regulation: forum domains – 50-250-kb chromosomal regions possessing coordinately expressed genes, *Biochemistry* (Moscow), **83**, 437-449.
16. Fishman, V. S., Salnikov, P. A., and Battulin, N. R. (2018) Interpreting chromosomal rearrangements in the context of 3-dimensional genome organization: a practical guide for medical genetics, *Biochemistry* (Moscow), **83**, 393-401.
17. Podgornaya, O. I., Ostromyshenskii, D. I., and Enukashvily, N. I. (2018) Who needs this garbage, or the dark matter of the genome, *Biochemistry* (Moscow), **83**, 450-466.
18. Iarovaia, O. V., Kovina, A. P., Petrova, N. V., Razin, S. V., Yudinkova, T. S., Vassetzky, Y. S., and Ulianov, S. V. (2018) Genetic and epigenetic mechanisms of β-globin gene switching, *Biochemistry* (Moscow), **83**, 381-392.
19. Sall, F. B., Germini, D., Kovina, A. P., Ribrag, V., Wiels, J., Toure, A. O., Iarovaia, O. V., Lipinski, M., and Vassetzky, Y. S. (2018) Effect of environmental factors on nuclear organization and transformation of human B lymphocytes, *Biochemistry* (Moscow), **83**, 402-410.
20. Moor, N. A., and Lavrik, O. I. (2018) Protein–protein interactions in DNA base excision repair, *Biochemistry* (Moscow), **83**, 411-422.
21. Putlyaev, E. V., Ibragimov, A. N., Lebedeva, L. A., Georgiev, P. G., and Shidlovskii, Y. V. (2018) Structure and functions of mediator complex, *Biochemistry* (Moscow), **83**, 423-436.
22. Sverdlov, E. D. (2018) Unsolvable problems of biology: it is impossible to create two identical organisms, to defeat cancer, and to map organisms onto their genomes, *Biochemistry* (Moscow), **83**, 370-380.