Институт по молекулярна
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Attitude by the Reviewer

By Professor Nina Atanassova, PhD, DSc,
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Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences (IEMPAM-BAS)

Re: defense of dissertation for acquisition of scientific degree "Doctor of Science" the Professional field 4.3. Biological Sciences, specialty "molecular biology" in the Roumen Tsanev Institute of Molecular Biology, Bulgarian Academy of Sciences

Author: Professor Stefan Ivanov Dimitrov, PhD in IMB-BAS

Title: The chromatin – from structure to function

Brief presentation of the author of the DSc dissertation

Professor Stefan Dimitrov, PhD, graduated from the Faculty of Physics at the University of St. Kliment Ohridski" in 1976 with a master's degree in solid-state physics. His scientific career started in the IMB, where he acquired the PhD degree in 1982 after defending a dissertation developed at the IMB and the Moscow Institute of Molecular Biology. After 1990, Prof. Dimitrov worked as a visiting professor in International Research Centers in Switzerland, Canada and the USA. From 1996 to 2017, he was a full professor DR1, Head of Lab "Epigenetics and Chromatin Biology" and Research Director of the Institute of Advanced Biosciences at CNRS and the University Grenoble, France. After that he remained as Emeritus Director of Research at CRNS, France. From 2018 to 2023, he was Research Director of Izmir Biomedicine and Genome Center, Turkey. Since 2023, he has been a full professor at IMB and Project Coordinator funded by "ERA Chair" of the Horizon Europe Framework Programme "Advanced epigenetics studies to increase the research and innovations capacity of the Roumen Tsanev Institute of Molecular Biology of the Bulgarian Academy of Sciences (AEGIS-IMB)". Prof. Dimitrov has published 157 articles, with over 12,000 citations and h-index 59. He has supervised over 90 doctoral and post-doctoral students. He was among the few founders of the interdisciplinary Institute "Laboratoire Joliot Curie" at Ecole Normale Supérieure de Lyon and the Izmir Biomedicine and Genome Center. He has been awarded 6 prestigious international awards for excellence in France, for which he has earned high international recognition as a top scientist in the world.

Timeliness and aims of the DSc dissertation

The author of the dissertation, Prof. Stefan Dimitrov, has dedicated his long term scientific carrier to the still undiscovered enigmas of the chromatin structure and plasticity, as well as DNA packaging and unfolding, and the role of histone protein variants as key epigenetic factors responsible for maintaining nuclear homeostasis. This is a fundamental topic with broad prospects for providing new knowledge for understanding structural epigenetics that is of global importance for science. On the other hand, these research priorities has clinical potential for elucidation of the epigenetic mechanisms of a number of pathological conditions - oncological diseases, inflammation and immune response, genetic diseases, etc.

In this respect, Prof. Dimitrov formulated two general goals: 1) About the nucleosome structure, associated with histone H1, and the 3D organization of the chromatin fiber by establishment of the crystal and cryo-electron microscopic structure of these objects; 2) About the role of histone proteins, through their replacement with variants of H2A (macroH2A, H2A.Bbd, H2A.Z) and H3 (CENP-A), in modulating the structural chromatin organization which allows the proper functioning of the nucleus. Thus the two goals are fully consistent with the topic of the dissertation.

Results, discussion and scientific contribution of the DSc dissertation

In general, the dissertation work is structured in an unconventional way with separate sections "Materials and Methods", "Results and Discussion", "Conclusions and Contributions". The publications used are presented and attached, which provides the advantage of direct information with the author's original data, on the one hand, and the relevance of the methodological approaches used to generate the original results and scientific achievements. The dissertation for "Doctor of Sciences" degree includes 16 articles published in world-renowned journals with an impact factor of over 10 - Nature, Molecular Cell, Nucleic Acids Research, Nature Structural & Molecular Biology, and Proceedings of the National Academy of Sciences, USA. Despite the obvious high contribution of the research, which is of global importance, I would recommend the author briefly to formulate the main scientific achievements. I would summarize them in two directions, corresponding to the goals of the work:

I. The 3D interactions of the different domains of the linker histone H1 with the nucleosome and linker DNA have been mapped and their role in inducing the more compact structure of the nucleosome has been established. This in turn stimulates the formation of an ordered structure and the condensation of the 30 nm chromatin fibril. The provided new insight into the interaction of H1 with the linker DNA and with the nucleosome is a breakthrough in structural chromatin epigenetics and sheds light on the understanding of how transcription factors can bind to DNA. The complex approach of biophysical, physicochemical and cryo-electron microscopic methods has allowed the author to detail the structure of the 30 nm chromatin fiber confirming the two-start model. This provides insight into how chromatin can switch between different conformations in response to small changes in the local environment (Mg^{2+} concentration).

In relation with these contributions, the first 5 publications are of used.

II. The second group of contributions are generated to fulfil the second goal of clarifying the role of histone variants H2A and H3 in genome organization and its function. For that purpose, the author's laboratory has generated a set of conditional knockout mouse lines (cKO) for macroH2A, H2A.Z, CENP-A and H3.3, as well as an in vivo model of knockout H2A.Z mice.

Regarding the role of H2A.Bbd, it has been found that it can replace the canonical H2A histone in the construction of the nucleosome particle, which can change its structure, reducing its stability and altering its remodelling capabilities (publications No. 7-9). The macroH2A variant affects nucleosome remodelling and can repress transcription by interfering the binding to the transcription factor NF-kB (publication No. 6).

The histone variant H2A.Z is the subject of more extensive and recent studies by the author, which reveal its role in the initiation of DNA double-strand break repair (publications No. 12-16). A contribution to clarifying the contradictory data in the literature about participation of H2A.Z in transcription activation is the discovery by Prof. Dimitrov that enrichment of H2A.Z on active promoters is a marker, but not an active driver of transcription in terminally differentiated muscle cells. The publication with these results was assessed as a breakthrough article of Nucleic Acids Research for 2020 (publication No. 14). The author has published in Nature the discovery of the first chaperone for H2A.Z, the ANP32E, and its molecular mechanism by which it removes H2A.Z from the nucleosomes (publication No. 12).

Publications 10 and 11 are dedicated to the histone H3 variant, CENP-A, and they contribute to the elucidation of its role in the structuring and functioning of chromosome kinetochores and the binding of CENP-A-nucleosomes to the linker histone H1.

Experiments with cKO mouse lines for the other histone variants are currently developed in the author's laboratory and preliminary data imply to some unexpected epigenetic roles of histone variants in nuclear homeostasis.

Conclusion

The presented DSc dissertation by Prof. Stefan Dimitrov is the essence of his long-term in-depth, interdisciplinary scientific research, defined in the world scientific literature as high-ranking, making a breakthrough in science. The candidate's creative searches are distinguished by their large scale and innovation and have been carried out by a high technological approach. Discovering the deep details in the structure and function of the genome are an indispensable contribution to the development of the second period of progress in molecular epigenetics after the discovery of the structure of DNA.

The spatial aspects of histone H1 contacts with the nucleosome and the functional significance of histone variants are the fundamentals upon which future strategies can be built to elucidate the epigenetic basis of nuclear processes in normal and pathological conditions.

All this gives me sufficient ground for excellent assessment of the dissertation thesis by Prof. Stefan Dimitrov entitled " The chromatin – from structure to function " and strongly recommend to the members of the Scientific Jury to vote positively for awarding of the scientific degree "Doctor of Sciences" to Prof. Stefan Dimitrov in the specialty "molecular biology", Professional field 4.3. "Biological Sciences".

27.01.2025

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