MASARYKOVA UNIVERZITA

Annex No. 11 to the MU Directive on Habilitation Procedures and Professor Appointment Procedures

Habilitation Thesis Reviewer's Report

Masaryk University Faculty	Faculty of Science
Procedure field	Genomics and proteomics
Applicant	RNDr. Martin Falk, Ph.D.
Applicant's home unit, institution	Institute of Biophysics of the Czech Academy of Sciences
Habilitation thesis	DNA Damage and Repair upon Cell Exposure to Different Types of Ionizing Radiation ? the Importance of Chromatin Context and New Perspectives of Cancer Radiotherapy
Reviewer	name and surname, including academic degrees
Reviewer's home unit, institution	Patrick J. Johnston Centre for Cancer Research, Queen's University Belfast…

This Habilitation Thesis focusses on the important role of chromatin structure in the DNA damage and repair response of cells to different types of ionizing radiation. It summarizes the seminal work of Dr Falk, an exceptional scientist, in this area. This is exemplified by the 37 high quality papers that cover the material presented in the Thesis delivering a significant impact to research in this area over a prolonged period of time, involving key international collaborators.

The overall contribution of this work is the presentation of a new model of the relationship between the radiation track structure, higher order chromatin structure, chromatin dynamics, sensitivity of structurally and functionally distinct chromatin domains to DNA damage, efficiency of DNA repair and mechanism of chromosome aberration formation. The work is presented around three groups of papers. The first of these covers the principles of higher-order chromatin organisation and its alterations during carcinogenesis. It highlights the significant advances in our knowledge of chromatin organisation which Dr Falk has contributed to. Relevant examples of the implications of this are described, such as oncogenic protein changes in chromatin structure leading to carcinogenesis and its importance in acute and chronic myeloid leukaemia and myelodysplastic syndromes.

The second focuses on the role of higher-order chromatin organization in DNA damage and repair. In particular, this makes seminal contributions to our understanding of the distributions of DSB in different chromatin domains and the interrelationship between DSB repair and chromosomal aberration formation. Much of the focus is on the complexity of DNA damage produced by different qualities of radiation, their interaction with chromatin structure and

DSB repair focus nanostructures with the high resolution assessment of this with state-of-the art single molecule localization microscopy (SMLM).

The third group focuses on tumour cell radioresistance and therapeutic approaches, both to sensitise cells with different radiation qualities and metal nanoparticle-based approaches. This has included the impact of irregular alternative splicing variants of BRCA1 on DNA repair and genomic stability. Further studies have followed repair in primocultures of Head and Neck cancers and their associated fibroblasts and the impact of radiation quality. Nanoparticle studies have shown an important role for lysosomal damage leading to apoptosis in irradiated cell culture models. Finally, a reported differential protection of amifostine in normal but not tumour cells, via an impact on DNA repair is reported.

Overall the Thesis summarises a substantive and wide-ranging contribution to our scientific knowledge in this area and confirms the major contribution that Dr Falk has made.

Reviewer's questions for the habilitation thesis defence (number of questions up to the reviewer)

An important aspect inferred by Dr Falk's work has been the potential interplay between chromatin structure and immune function which I would like to see discussed further at the Thesis Defence as this is a highly topical area of current and future research.

Conclusion

The habilitation thesis entitled "DNA Damage and Repair upon Cell Exposure to Different Types of Ionizing Radiation ? the Importance of Chromatin Context and New Perspectives of Cancer Radiotherapy" by RNDr. Petr Falk, Ph.D. ***fulfils*** requirements expected of a habilitation thesis in the field of Genomics and proteomics.

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