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From genomics to spatio-temporal organization of cellular processes: What can confocal microscopy tell us about the mechanism of DNA repair and formation of chromosomal translocations?

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Abstract

We show how confocal microscopy can contribute to the research of DNA double-strand break (DSB) repair and propose a model of the relationship between the higher-order chromatin structure, DSB induction, repair, and formation of chromosomal translocations.

The integrity of the human genome is continuously threatened by intercellular and environmental factors. DSBs represent the most serious DNA lesions – even a single DSB can initiate cell death or cancer when repaired inaccurately. On the other hand, tumor cells are most efficiently killed by DSBs introduced by radiotherapy or chemotherapy.

Until recently, mainly the "biochemical" aspects of DSB repair were studied. Today, in the era of genomics, we have quite detailed information how dozens of proteins interact in the frame of complex signaling and repair pathways (or rather networks) in order to preserve the genome integrity. However, how these processes are orchestrated in time and space of the cell nucleus is largely unknown.

We have employed a high-resolution confocal microscopy (in combination with protein labeling in spatially fixed and living cells) to study how DSBs are being repaired in the context of nuclear architecture. We will discuss how chromatin structure influences the activity, mechanism and fidelity of DSB repair.

For instance, heterochromatin must decondense to allow DSB rejoining. However, this decondensation also increases DSB movement - "directed" by the higher-order chromatin structure - that might increase the risk of chromosomal translocations.

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Biography

Martin Falk has completed his Ph.D from Masaryk University in Brno, CR. He is the leader of the Department of Chromatin Function, Damage and Repair at the Institute of Biophysics of ASCR, Brno,CR. He participated in more than 25 papers that concern the role of higher-order chromatin structure in regulation of cellular processes. Other research interests include the DNA double-strand break repair, carcinogenesis, tumor cells radio-sensitization, and radiobiology.

Important publications: Falk et al. BBA-MCR 1773/10(2007), BBA-MCR 1783/12(2008), Mutation Research 704(2010), Applied Radiation and Isotopes (2013); Lukasova et al., BBA-MCR 1833/3(2013); Ježková et al., Applied Radiation and Isotopes (2013).