Laboratory of Genome Integrity

DNA damage response, cytokines, cellular senescence, cancer, ageing

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Realization of complex tasks of living organisms depends on the information stored in DNA of their genomes. The loss of this information due to endogenous and exogenous physicochemical damage to DNA results in disintegration of homeostasis at the cellular and organism levels manifested as diseases, including cancer and ageing. Several tightly orchestrated mechanisms take care of preserving the intactness of genetic information by preventing and repairing DNA damage. Our research is centred on cellular responses (collectively termed DNA damage response; DDR) to DNA double-strand breaks, presumably the most deleterious lesions affecting DNA. Cells with unhealed chromosomal breaks are mostly prevented from cell division due to activated DNA damage cell cycle checkpoints; however, following unscheduled cell division, unrepaired breaks result in chromosomal instability with accompanying changes in gene dosage – the driving force of malignant transformation. Specifically, we focus on 1) posttranslational modifications (phosphorylation, ubiquitylation, sumoylation and acetylation) of key players involved in sensing and transmitting signals from DNA breaks to cellular effectors responsible for activation of cell cycle checkpoints and repair; 2) mechanisms of radioresistance and chemoresistance of cancer cells; 3) mechanisms of cellular response to persistent irreparable DNA damage lesions manifested as irreversible cell cycle arrest (cellular senescence); 4) role of DNA damage-induced expression of secreted factors (cytokines) in autocrine/paracrine signalling and intercellular communication; and 5) impact of the above mechanisms on cancer and ageing with the aim to find new therapeutic approaches, such as thermotherapy using targeted gold nanoparticles. To summarize our main recent findings, we have functionally characterized two proteins (UBA1 and Nup153) identified previously during high-throughput siRNA-based phenotypic screening of factors involved in posttranslational modifications of DDR components. We have found that the IL6-STAT3 signalling pathway is involved in transcription regulation of PML tumour suppressor via autocrine/paracrine mechanisms. We have found that persistent DNA damage and resulting cellular senescence is transmittable to surrounding cells via factors secreted from damaged cells (so-called bystander senescence). Currently, we are characterizing mechanisms of radioresistance and chemoresistance of prostate metastatic cancer cells and we are screening DNA and RNA aptamers utilisable for targeting of gold nanorods to cancer cells by the use of a selection procedure based on Cell-Selex.

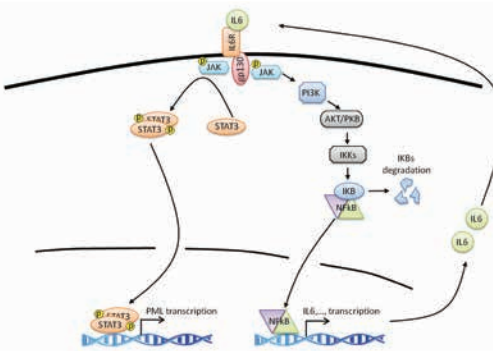

Fig. 1. Role of autocrine/paracrine IL6/STAT3 and NFκB signalling pathways in transcription regulation of tumour suppressor PML.

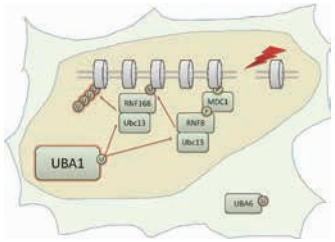

Fig. 2. Involvement of UBA1 in ubiquitination of factors recruited to the site of DNA double-strand breaks.

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- GA CR, GPP305/10/P420 - Role of Wip1 phosphatase in the DNA damage response, 2010-2012, L. Macůrek
- GA CR, GPP305/11/P683 - Post-translational modifications of Daxx and their functional relevance in DNA damage response and cellular senescence, 2011-2013, H. Hanzlíková
- GA CR, GAP305/12/2485 - Structure and function of proteins involved in DNA damage signalling, 2012-2015, L. Macůrek
- GA CR, GA204/09/0565 - Role of RECQ5 DNA helicase in maintenance of genomic stability, 2009-2013, P. Janščák
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