LABORATORY OF

GENOME INTEGRITY

DNA damage response, carcinogenesis, ageing, R-loops, gold nanoparticles

Jiří Bartek

more information

e-mail

The long-term research interest of our group is focused on cellular responses to DNA damage, namely complex and/or difficult to repair DNA lesions resulting in permanent block of cell division termed cellular senescence. Cellular senescence, by its impact on the tissue microenvironment mediated by secretion of specific factors involving proinflammatory cytokines, is emerging as key of multiple factors contributing to ageing and ageing-associated diseases including cancer. We are specifically interested in 1) highlighting the nature of complex and irreparable DNA lesions characteristic of senescent cells; 2) deciphering the role of ribosomal DNA instability in development of cellular senescence and the function of promyelocytic leukaemia protein (PML) in DNA repair of ribosomal DNA loci; 3) unravelling the phenotypic changes occurring during cellular senescence that contribute to resistance of senescent cells to cell death and oxidative stress; 4) mechanisms how senescent cells contribute to radioresistance and chemoresistance of cancer cells and cancer cell phenotypic plasticity in general, including function of specific signalling pathways (namely interferon and TGF-β) in these processes; 5) mechanisms resolving collisions between replication and transcription machineries and associated RNA:DNA hybrids referred to as R-loops; and 6) involvement of the above mechanisms in pathological changes manifested as cancer and ageing with the goal to develop novel therapeutic means, such as development of new drugs specifically targeting senescent cells (termed senolytics) and nanotechnology-based approaches, for instance, thermotherapy utilising targeted gold nanoparticles.

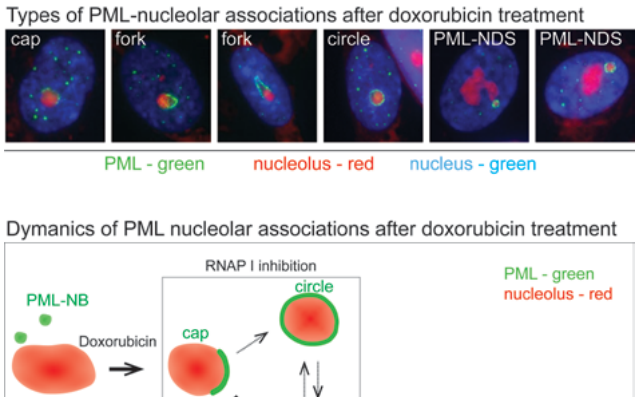

Figure 1. Promyelocytic leukaemia protein (PML) is a core and essential component of PML nuclear bodies (PML-NBs) that are functionally involved in the regulation of cell cycle, apoptosis and cellular senescence. We found that after specific treatments causing drug-induced senescence, PML interacts with the surface of the nucleolus, as shown in the upper microscopic image where PML (green) was detected by indirect immunofluorescence; the nucleolus and nucleus are marked by TOTO3 (red) and DAPI (blue). Schematic depiction (bottom part) of doxorubicin-induced dynamic transitions of nucleolar PML compartments obtained by long-term following cells expressing fluorescent proteins EGFP-PML IV (green) and nucleolar marker RFP-B23 (red) by time lapse microscopy in relation to nucleolar activity of RNA polymerase I (RNAP I). PML-NDS, PML nucleolus-derived structure; PML-NB, PML nuclear body.

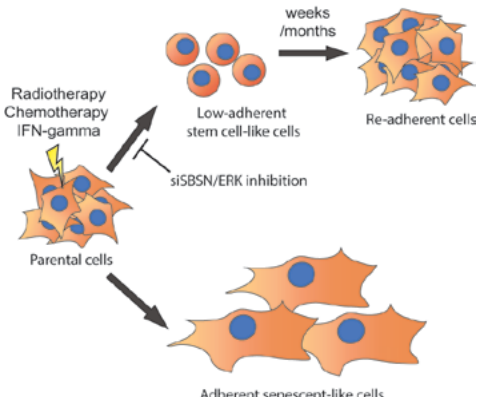

Figure 2. Most cancer patients experience tumour recurrence and metastatic dissemination even after radio- or chemo-therapy. Transcriptome profiling of cancer cells surviving radiation or chemotherapy revealed that, in low-adherent stem-like cells, an IFN- and MAPK/ERK-driven transcription programme mediated expression of a novel oncoprotein, suprabasin, that is functionally involved in the survival of low-adherent cells.

Selected publications:

1. Hubackova S, Pribyl M, Kyjacova L, Moudra A, Dzijak R, Salovska B, Strnad H, Tambor V, Imrichova T, Svec J, Vodicka P, Vaclavikova R, Rob L, Bartek J*, Hodny Z* (2019). Interferon-regulated suprabasin is essential for stress-induced stem-like cell conversion and therapy resistance of human malignancies. *Mol Oncol*, **13**:1467-1489.
2. Imrichova T, Hubackova S, Kucerova A, Kosla J, Bartek J*, Hodny Z*, Vasicova P* (2019) Dynamic PML protein nucleolar associations with persistent DNA damage lesions in response to nucleolar stress and senescence-inducing stimuli. *Aging*, **11**:7206-7235.
3. Vajrychova M, Salovska B, Pimkova K, Fabrik I, Tambor V, Kondelova A, Bartek J*, Hodny Z* (2019) Quantification of cellular protein and redox imbalance using SILAC-iodoTMT methodology. *Redox Biol*, **24**:101227.
4. Vancurova M, Hanzlikova H, Knoblochova L, Kosla J, Majera D, Mistrik M, Burdova K, Hodny Z*, Bartek J* (2019) PML nuclear bodies are recruited to persistent DNA damage lesions in an RNF168-53BP1 dependent manner and contribute to DNA repair. *DNA Repair (Amst)*, **78**:114-127.
5. Zarska M, Sramek M, Novotny F, Havel F, Babelova A, Mrazkova B, Benada O, Reinis M, Stepanek I, Musilek K, Bartek J, Ursinyova M, Novak O, Dzijak R, Kuca K*, Proska J*, Hodny Z* (2018) Biological safety and tissue distribution of (16-mercaptohexadecyl)trimethylammonium bromide-modified cationic gold nanorods. *Biomaterials*, **154**:275-290.

In the picture: 1. Přibyl Miroslav | 2. Šalovská Barbora | 3. Andrš Martin | 4. Salajková Šárka | 5. Imrichová Terezie | 6. Cuchalová Lucie | 7. Žárská Monika | 8. Boleslavská Barbora | 9. Kondelová Alexandra | 10. Vašicová Pavla | 11. Kubíková Iva | 12. Naščáková Zuzana | 13. Oravetzová Anna | 14. Ryšánek David | 15. Vančurová Markéta | 16. Opravilová Magdaléna