LABORATORY OF

GENOME INTEGRITY

DNA damage, cellular senescence, glioma, cancer resistance, PML

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Cells with unfinished DNA damage signalling (uDDS) caused by complex or difficult to repair DNA damage (called senescent cells) secrete a diverse set of factors, including pro-inflammatory cytokines and TGF beta family morphogens with multifaceted impact on surrounding tissues. The composition of this secretome, termed senescence-associated secretory phenotype (SASP), is shaped by numerous factors including nature of DNA-damaging stimulus, cell type and metabolic state, and cell-to-cell interaction in surrounding tissues; therefore, the composition of SASP has to be studied for each specific biological condition. The importance of studying SASP to uncover the pathogenesis of human diseases comes from studies including ours demonstrating, for instance, its impact on malignant features of cancer cells such as proliferation, invasiveness and migration, cancer stem cell mobilization, and therapeutic resistance. Analyses of secretomes directly in tissues are currently technically challenging. New methods and approaches have to be developed to decipher the complex information exchange among cells in the organism and its impact on homeostasis.

Our research includes understanding the molecular mechanisms leading to uDDS, cellular responses to uDDS, including phenotypic manifestation of the altered secretory milieu in response to uDDS, and defining molecular targets to develop new therapeutic approaches.

Running projects:

1) Understanding the nature of complex/unrepaired DNA damage

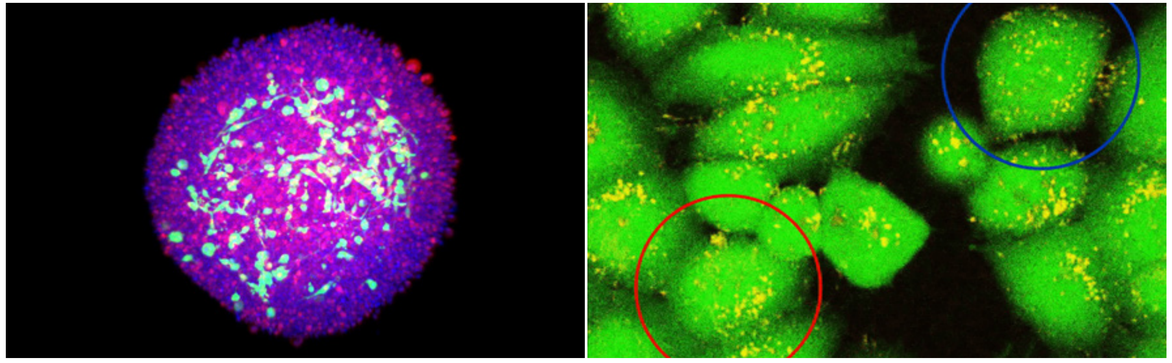
Besides telomeres, ribosomal DNA (rDNA) loci represent repetitive DNA sequences being difficult to repair. We focus on specific mechanisms damaging rDNA loci, their repair, stability and role in tumorigenesis.

2) Role of the tissue microenvironment in glioma therapeutic resistance

High-grade gliomas belong to less treatable human malignant tumours. In cooperation with Karolinska Institute, Sweden, and medical faculties of Masaryk University, Brno and Palacky University, Olomouc, we seek to reveal the molecular mechanisms behind glioma therapeutic resistance.

3) Development of new drugs and nanotherapeutics

In frame of the cooperation network including University Hospital of Hradec Kralove, Czech Technical University in Prague, and Second Faculty of Medicine, Charles University, Prague we are developing new compounds with anti-tumour and anti-aging properties (senolytic and senomodulatory drugs) and nanotechnology-based approaches for cancer treatment.



Left: 3-D glioma spheroid developed as a model to study interactions among cancer (red) and senescent (green) cells (visualized by light sheet microscopy; cell nuclei in blue). Right: Demonstration of thermotherapy by gold nanorods (yellow) in cancer cells induced by near infrared light (920 nm) produced by femto second laser. Cell death by apoptosis (blue circle) and necrosis (red circle) were detected by membrane blebbing and loss of calcein fluorescence (green), respectively.

Selected publications:

1. Hornofova, T., B. Pokorna, S.S. Hubackova, A. Uvizl, J. Kosla, J. Bartek*, Z. Hodny*, and P. Vasicova*. 2022. Phospho-SIM and exon8b of PML protein regulate formation of doxorubicin-induced rDNA-PML compartment. DNA Repair. 114:103319.
2. Kosar, M., M. Giannattasio, D. Piccini, A. Maya-Mendoza, F. García-Benítez, J. Bartkova, S.I. Barroso, H. Gaillard, E. Martini, U. Restuccia, M.A. Ramirez-Otero, M. Garre, E. Verga, M. Andújar-Sánchez, S. Maynard, Z. Hodny, V. Costanzo, A. Kumar, A. Bachi, A. Aguilera, J. Bartek*, and M. Foiani*. 2021. The human nucleoporin Tpr protects cells from RNA-mediated replication stress. Nature communications. 12:3937.
3. Pribyl, M., S. Hubackova, A. Moudra, M. Vancurova, H. Polackova, T. Stopka, A. Jonasova, R. Bokorova, O. Fuchs, J. Stritesky, B. Salovska, J. Bartek*, and Z. Hodny*. 2020. Aberrantly elevated suprabasin in the bone marrow as a candidate biomarker of advanced disease state in myelodysplastic syndromes. Molecular Oncology. 14:2403-2419.
4. Rysanek, D., P. Vasicova, J.N. Kolla, D. Sedlak, L. Andera, J. Bartek*, and Z. Hodny*. 2022. Synergism of BCL-2 family inhibitors facilitates selective elimination of senescent cells. Aging. 14:6381-6414.
5. Salovska, B., A. Kondelova, K. Pimkova, Z. Liblova, M. Pribyl, I. Fabrik, J. Bartek, M. Vajrychova*, and Z. Hodny*. 2022. Peroxiredoxin 6 protects irradiated cells from oxidative stress and shapes their senescence-associated cytokine landscape. Redox biology. 49:102212.