LABORATORY OF

GENOME DYNAMICS

DNA single-strand breaks, ADP-ribosylation, RNA metabolism, neurological disease

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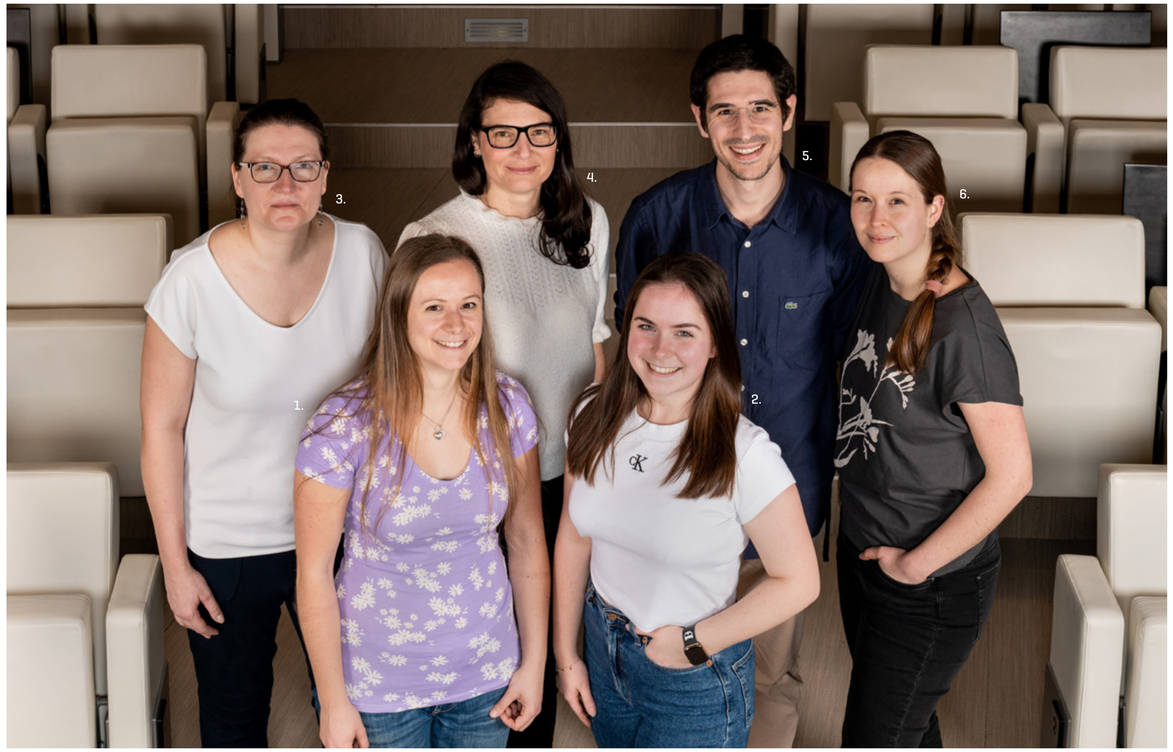
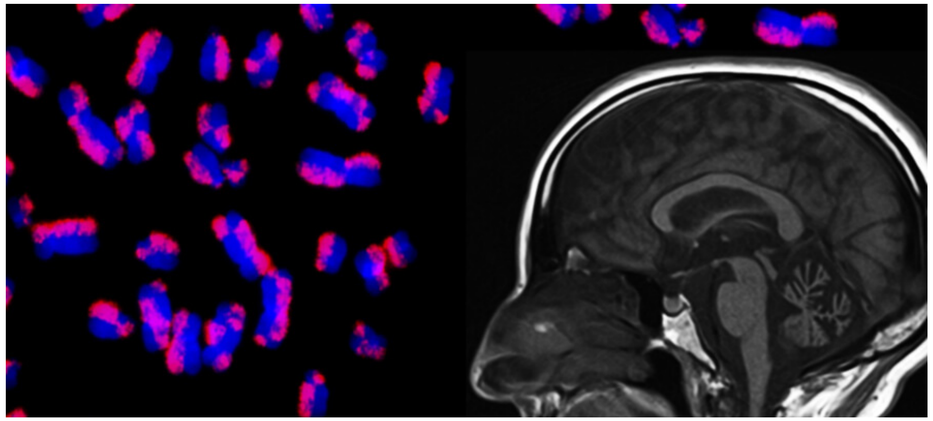


In the picture: 1. Ilievová Kristýna | 2. Bronišová Denisa | 3. Burdová Kamila | 4. Hanzlíková Hana | 5. Pizarro Madureira Salgado De Oliveira Gonçalo | 6. Cihlářová Zuzana

ADP-ribosylation is a ubiquitous transient post-translational modification of proteins that is involved in a number of major cellular and biological processes, including DNA damage repair, cell proliferation and differentiation, metabolism, stress and immune responses. The main research of our group is focused on ADP-ribosyl transferases; a class of DNA repair enzymes that detect DNA single-strand breaks (SSBs) and signal their presence by catalysing the rapid synthesis of mono(ADP-ribose) and poly(ADP-ribose) and hydrolases; enzymes that catalyse the removal of specific ADP-ribosyl modifications from proteins. SSBs are amongst the most frequent DNA lesions arising in cells that might interfere with RNA processing and transcription and if not repaired correctly can threaten both genetic stability and cell survival. Notably, defects in DNA SSB repair, ADP-ribose metabolism, RNA processing and transcription regulation are associated with hereditary neurodevelopmental and neurodegenerative diseases in human, underscoring the particular importance of these processes in long-lived post-mitotic neurons. We investigate the molecular mechanisms by which DNA SSBs are detected and repaired and we are especially interested in identifying and characterising the protein factors and pathways that couple aberrant ADP-ribose metabolism to neurodegenerative disease. We aim to examine whether the deregulated ADP-ribose metabolism at sites of SSBs extends beyond rare DNA repair-defective diseases to dementia, a neurodegenerative disease that presents the greatest threat to normal human ageing and human health. The risk of being affected by a neurodegenerative disease increases dramatically with age. Although treatments may help relieve some of the physical or mental symptoms associated with neurodegenerative diseases, there are currently no known cures. Therefore, there is a critical need to improve our understanding of what causes neurodegeneration and to develop new approaches for treatment and prevention. The cause of neurodegenerative disorders is often genetic; however, the involved genes and the underlying mechanisms are increasingly diverse, indicating the complexity of brain development and growth. Ultimately, we envisage that our work will lead to new therapeutic avenues for clinical treatment of human neurodegenerative disease.



Left: Increased sister chromatid exchange, the exchange of genetic material between two identical sister chromatids, in cells from a patient suffering from neurodegeneration with defects in the single-strand break repair pathway. Right: Magnetic Resonance Imaging (MRI) scan showing a patient suffering from neurodegeneration with cerebellar atrophy.

Selected publications:

1. Cihlarova Z, Kubovciak J, Sobol M, Krejcikova K, Sachova J, Kolar M, Stanek D, Barinka C, Yoon G, Caldecott KW, Hanzlikova H*: BRAT1 links Integrator and defective RNA processing with neurodegeneration. Nat Commun 2022 13(1): 5026.
2. Vaitsiankova A, Burdova K, Sobol M, Gautam A, Benada O, Hanzlikova H*, Caldecott KW*: PARP inhibition impedes the maturation of nascent DNA strands during DNA replication. Nat Struct Mol Biol 2022 29(4):329-338.
3. Wu W, Hill SE, Nathan WJ, Paiano J, Callen E, Wang D, Shinoda K, van Wietmarschen N, Colón-Mercado JM, Zong D, De Pace R, Shih HY, Coon S, Parsadanian M, Pavani R, Hanzlikova H, Park S, Jung SK, McHugh PJ, Canela A, Chen C, Casellas R, Caldecott KW*, Ward ME*, Nussenzweig A*: Neuronal enhancers are hotspots for DNA single-strand break repair. Nature 2021 593(7859): 440-444.
4. Hanzlikova H*, Prokhorova E, Krejcikova K, Cihlarova Z, Kalasova I, Kubovciak J, Sachova J, Hailstone R, Brazina J, Ghosh S, Cirak S, Gleeson JG, Ahel I, Caldecott KW*: Pathogenic ARH3 mutations result in ADP-ribose chromatin scars during DNA strand break repair. Nat Commun 2020 11(1): 3391.
5. Kalasova I, Hailstone R, Bublitz J, Bogantes J, Hofmann W, Leal A, Hanzlikova H*, Caldecott KW*: Pathological mutations in PNKP trigger defects in DNA single-strand break repair but not DNA double-strand break repair. Nucleic Acids Res 2020 48(12): 6672-6684.