LABORATORY OF

GENOME DYNAMICS

DNA strand breaks, RNA processing, neurodegeneration

Keith W. Caldecott

more information

e-mail

The main research of our group is focused on Poly-ADP-Ribose Polymerases (PARPs); a class of DNA repair enzymes that detect DNA single-strand breaks (SSBs) and signal their presence by catalysing the rapid synthesis of poly(ADP-ribose). In the last few years, we have successfully developed a highly sensitive poly(ADP-ribose) assay for detecting SSBs that arise in the cells. This helped us to publish our conceptually ground-breaking discovery that the neurological disease that is triggered by unrepaired SSBs is caused in part by excessive activation of the DNA damage sensor protein, PARP1. This discovery identifies PARP1 as a plausible new therapeutic target in the treatment of neurological disease; a truly exciting concept in which novel and/or existing PARP1 inhibitors might be repurposed beyond their current use in the cancer clinic. Excitingly, excessive PARP activity has now also been implicated in several common neurological diseases including Alzheimer's, Parkinson's and Huntington's disease, expanding the possible translational significance of our finding. Ultimately, we suggest that SSBs might even be an aetiological factor in normal human ageing.

Importantly, our work in the field of PARP biology extends beyond the molecular mechanisms of human disease in postmitotic cells to include disease mechanisms in proliferating cells. In particular, we have recently identified that the primary source of endogenous SSBs that are detected by PARP1 during normal cell division are not stochastic DNA lesions, but instead are normal Okazaki fragment intermediates of DNA replication. This unexpected and striking discovery implicates PARP-dependent DNA repair as an alternative pathway for the processing of canonical DNA replication intermediates; a paradigm-shifting discovery that challenges the "text book" view of how DNA is replicated. This work has major implications for cancer research, because it identifies these obligatory DNA replication intermediates as the likely source of synthetic lethality that is triggered in certain cancer cells by PARP1 inhibition.

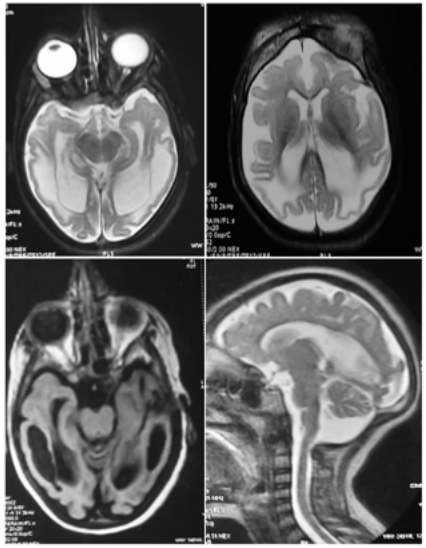

Figure 1. A magnetic resonance imaging (MRI) scan of a patient with microcephaly, an abnormally small head circumference.

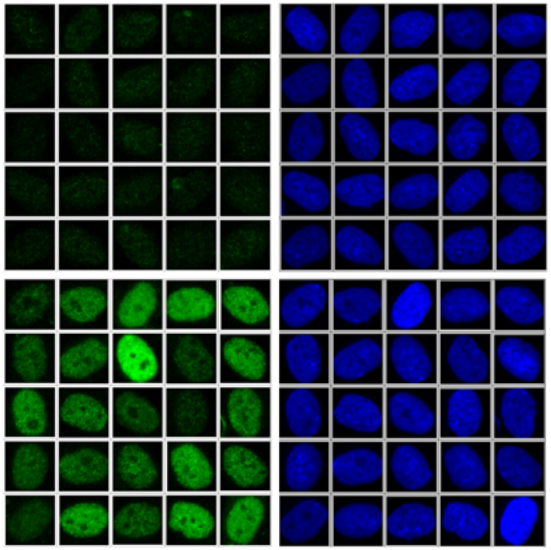

Figure 2. A fluorescence image obtained by high-throughput microscopy showing an accumulation of a DNA single-strand break marker ADP-ribose (green) in individual cell nuclei. After application of a DNA damage-inducing agent, the patient-derived cells (bottom) accumulate ADP-ribose compared to the healthy control (top).

Selected publications:

1. Hanzlikova H*, Kalasova I, Demin AA, Pennicott LE, Cihlarova Z, Caldecott KW* (2018) The importance of Poly(ADP-Ribose) Polymerase as a sensor of unligated Okazaki fragments during DNA replication. *Mol Cell*, **71(2)**:319-331.e3.
2. Hanzlikova H*, Caldecott KW* (2019) Perspectives on PARPs in S phase. *Trends Genet*, **35**:412-422.
3. Caldecott KW (2019) XRCC1 protein; form and function. *DNA Repair*, **81**:102664.
4. Kalasova I, Hanzlikova H*, Gupta N*, Li Y, Altmüller J, Reynolds JJ, Stewart GS, Wollnik B, Yigit G, Caldecott KW* (2019) Novel PNKP mutations causing defective DNA strand break repair and PARP1 hyperactivity in MCSZ. *Neurol Genet*, **5**:e320.
5. Mahjoub A, Cihlarova Z, Tétreault M, MacNeil L, Sondheimer N, Caldecott KW, Hanzlikova H*, Yoon G* (2019) Homozygous pathogenic variant in associated with nonprogressive cerebellar ataxia. *Neurol Genet*, **5**:e359.

In the picture: 1. Hanzlíková Hana | 2. Sobol Margarita | 3. Kalasová Ilona | 4. Krejčíková Kateřina | 5. Havelková Jarmila | 6. Caldecott Keith | 7. Cihlářová Zuzana