SZILVIA JUHÁSZ

Biological Research Centre
Department of Genetics

Address: Temesvári krt 62., H-6726 Szeged, Hungary

RESEARCH AREA

DNA double-strand breaks (DSBs) are among the most severe types of genomic damage threatening cellular viability. They can be repaired by two major pathways: canonical non-homologous end-joining (c-NHEJ) and homologous recombination (HR).

One of the earliest events upon DNA damage is the recruitment and activation of poly(ADP-ribose) polymerase 1 (PARP1), a key regulator of the DNA damage response. PARP1 is a DNA damage sensor and signal transducer that synthesizes negatively charged, branched poly(ADP-ribose) chains (PARylation) on target proteins. PARylation facilitates the recruitment of DNA repair factors and chromatin remodeling enzymes around damaged DNA. A little over a decade ago, it was discovered that BRCA1 and BRCA2 defective tumors can be specifically killed by PARP inhibitors (PARPi). This synthetic lethality had great premise in oncology because carriers of deleterious heterozygous germline mutations in the BRCA1 or BRCA2 genes have a high risk of developing breast and ovarian cancers. Regulatory bodies including FDA and EMA have recently accepted PARPi to be used in ovarian cancer patients with BRCA1 or BRCA2 mutations. Today, more than one PARP inhibitor is approved for cancer therapy.

PARP inhibitors drive synthetic lethality in two, not necessarily exclusive ways: interfering with DNA damage repair or trapping PARP on DNA. Both PARP1 and BRCAs play an important role in restarting stalled replication forks. Furthermore, the loss of 53BP1 in BRCA1 mutant cells alleviates hypersensitivity to PARP inhibitors and restores HR suggesting a role for PARP1 in regulating the choice between HR and NHEJ DNA repair pathways. Activated PARP1 strongly PARylates itself, which facilitates its own release from the damaged DNA, hence, the release of drug-inhibited PARP1 is hindered. In our studies we identify new factors that can modulate the PARPi-mediated synthetic lethality in human cells. We characterize these factors in classical molecular biology assays that can provide data to extend the therapeutic spectrum of PARP inhibitor treatment.

TECHNIQUES AVAILABLE IN THE LAB

Techniques for vertebrate cell lines including generation of KO cell lines with CRISPR, Western blot, co-immunoprecipitation assay, Southern blot, chromosome preparation, chromatin fractionation, immunostaining, laser microirradiation assay, micropore irradiation assay, SNAP-system for protein repopulation, measuring of the DNA repair kinetics, live cell imaging of fluorescently tagged proteins. In vitro techniques including recombinant DNA technology, protein purification and pull-down assays.

SELECTED PUBLICATIONS

Smith, R., Lebeaupin, T., **Juhász, S.**, Chapuis, C., D'Augustin, O., Dutertre, S., Burkovics, P., Biertümpfel, C., Timinszky, G., Huet, S. (2019) Poly(ADP-ribose)-dependent chromatin unfolding facilitates the association of DNA-binding proteins with DNA at sites of damage. **Nucleic Acids Res. 47:** 11250.

Elbakry, A., **Juhász, S.**, Mathes, A., Löbrich, M. (2018) DNA repair synthesis and histone deposition partner during homologous recombination. **Mol Cell Oncol. 5:** 1511210

Juhász, S., Elbakry, A., Mathes, A., Löbrich, M. (2018) ATRX Promotes DNA Repair Synthesis and Sister Chromatid Exchange during Homologous Recombination. **Mol Cell. 71:** 11.

Biehs, R., Steinlage, M., Barton, O., **Juhász, S.**, Künzel, J., Spies, J., Shibata, A., Jeggo, P.A., Löbrich, M. (2017) DNA Double-Strand Break Resection Occurs during Non-homologous End Joining in G1 but Is Distinct from Resection during Homologous Recombination. **Mol Cell. 65:** 671.

Burkovics, P., Dome, L., **Juhasz, S.**, Altmannova, V., Sebesta, M., Pacesa, M., Fugger, K., Sorensen, C.S., Lee, M.Y., Haracska, L., Krejci, L. The PCNA-associated protein PARI negatively regulates homologous recombination via the inhibition of DNA repair synthesis. (2016) **Nucleic Acids Res. 44:** 3176.