

GYULA TIMINSZKY

Senior Research fellow



HUN-REN Biological Research Centre
Department of Genetics

TITLE OF HIS PRESENTATION

Immortals, zombies and the fight against cancer

RESULTS FOR THE TALENTUM PRIZE 2026 NOMINATION

Identification of novel molecular mechanisms that determine cancer cell response to PARP inhibitors

RESEARCH AREA

Genome integrity is crucial for all living organisms. If damaged DNA is not promptly repaired, the mutations ultimately lead to the development of cancer. Defective repair can also cause immunodeficiency, neurodegenerative disorders and premature ageing. The range of DNA lesions require diverse signaling and repair pathways to shape the DNA damage response. This involves changes in nuclear dynamics including alterations in chromatin structure, nucleocytoplasmic transport and protein activities. ADP-ribosylation is one of the earliest post-translational modifications appearing upon DNA damage. Its effects are numerous. One of its functions is to relax chromatin at the sites of DNA damage, facilitating the access of DNA repair processes to the lesions. Our findings indicate that nuclear dynamics, mRNA metabolism and chromosome organization strongly depend on nuclear ADP-ribosylation reactions and their crosstalk with other signaling pathways. Its deregulation impairs DNA repair and is implicated in cancer. At the bedside, the inhibition of ADP-ribosylation by drugs is used to treat cancer with certain gene mutations. Our research goal is to characterize novel molecular mechanisms that regulate the DNA damage response, including nucleocytoplasmic transport, mRNA metabolism and chromatin architecture. We study novel cancer relevant mutations that are sensitive to ADP-ribosylation inhibitors, which could be potentially used to treat tumors carrying such mutations. Furthermore, we investigate the molecular basis of a novel DNA damage-induced nuclear export mechanism that regulates ADP-ribose metabolism.

TECHNIQUES AVAILABLE IN THE LAB

Molecular biology techniques for DNA, RNA and protein production, isolation and measurement, PCR, qPCR, cloning, sequencing, in vitro mutagenesis, Western blot, immunohistochemistry, cell culture methods, cell-based reporter assays to measure DNA repair, ADP-ribosylation, chromatin structure or protein-protein interaction, confocal microscopy, live cell imaging of fluorescently tagged proteins, knocking out or silencing genes in human cells, CRISPR-based whole genome knockout screening.

SELECTED PUBLICATIONS

- Smith, R., Sellou, H., Chapuis, C., Huet, S., **Timinszky, G.** (2018) CHD3 and CHD4 recruitment and chromatin remodeling activity at DNA breaks is promoted by early poly(ADP-ribose)-dependent chromatin relaxation. **Nucleic Acids Research** **46**: 6087.
- Singh, H.R., Nardoza, A.P., Möller, I.R., Knobloch, G., Kistemaker, H.A.V., Hassler, M., Harrer, N., Blessing, C., Eustermann, S., Kotthoff, C., Huet, S., Mueller-Planitz, F., Filippov, D.V., **Timinszky, G.**, Rand, K.D., Ladurner, A.G. (2017) A Poly-ADP-Ribose Trigger Releases the Auto-Inhibition of a Chromatin Remodeling Oncogene. **Molecular Cell** **68**: 860.
- Golia, B., Moeller, G.K., Jankevicius, G., Schmidt, A., Hegele, A., Preißer, J., Tran, M.L., Imhof, A., **Timinszky, G.** (2017) ATM induces MacroD2 nuclear export upon DNA damage. **Nucleic Acids Research** **45**: 244.
- Czarna, A., Berndt, A., Singh, H.R., Grudziecki, A., Ladurner, A.G., **Timinszky, G.**, Kramer, A., Wolf, E. (2013) Crystal structures of Drosophila Cryptochrome and mouse. Cryptochrome1: insights into circadian function. **Cell** **153**: 1394.
- Jankevicius, G., Hassler, M., Golia, B., Rybin, V., Zacharias, M., **Timinszky, G.**, Ladurner, A.G. (2013) A family of macrodomain proteins reverses cellular mono-ADP-ribosylation. **Nature Structural & Molecular Biology** **20**: 508.