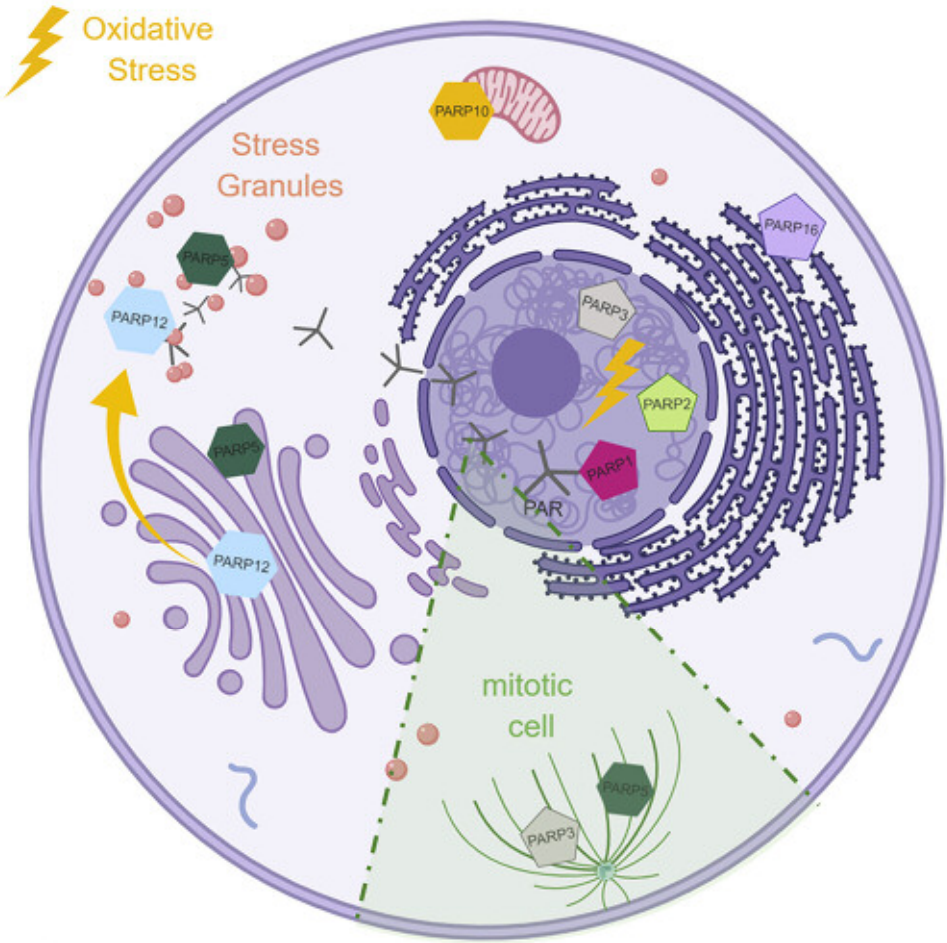
Abstracts of papers presented
at the 2020 *virtual* meeting on

THE PARP FAMILY & ADP-RIBOSYLATION

December 9–December 11, 2020



CSH Cold Spring Harbor Laboratory
MEETINGS & COURSES PROGRAM

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at the 2020 *virtual* meeting on

THE PARP FAMILY & ADP-RIBOSYLATION

December 9–December 11, 2020

Arranged by

W. Lee Kraus, *UT Southwestern Medical Center*
Andreas Ladurner, *Ludwig-Maximilians-University, Germany*
Susan Smith, *Skirball Institute NYU School of Medicine*

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PROGRAM

WEDNESDAY, December 9—10:00 AM US EST

SESSION 1 PARPs IN PHYSIOLOGY AND DISEASE

Chairpersons: **Daniela Corda,** Italian National Research Council, Naples
Michael Cohen, Oregon Health and Science University, Portland

Silencing of PARP2 blocks autophagic degradation
Laura Jankó, Zsanett Sári, Tünde Kovács, Gréta Kis, Magdolna Szántó, Miklós Antal, Gábor Juhász, Peter Bai.
Presenter affiliation: University of Debrecen, Debrecen, Hungary. 1

Regulation of transcription elongation through the PARP1 interacting protein PHF3
Lisa-Marie Appel, Dea Slade.
Presenter affiliation: Max Perutz Labs, University of Vienna, Vienna, Austria. 2

Necrosis inhibitor, IM-54, reduces oxidative stress-induced cell death and injury in *Arh1*-deficient cells and mice
Jiro Kato, Hiroko Ishiwata-Endo, Xiangning Bu, Jianfeng Zhu, Joel Moss.
Presenter affiliation: Pulmonary Branch, Bethesda, Maryland. 3

Alphavirus ADP-ribosylhydrolase activity disrupts stress granule formation
Aravinthkumar Jayabalan, Diane E. Griffin, Anthony K. Leung.
Presenter affiliation: Johns Hopkins University, Baltimore, Maryland. 4

Regulation of hypoxia-inducible factor stability and activation by tankyrases
Esteban Zamudio-Martínez, Daniel Delgado-Bellido, Ángel García-Díaz, Jose M. Rodríguez-Vargas, Javier Oliver-Pozo.
Presenter affiliation: Instituto de Parasitología y Biomedicina López Neyra, CSIC and CIBERONC, Instituto Salud Carlos III, Granada, Spain. 5

PARP-1 and splicing
Elena Matveeva, Manana Melikishvili, Yvonne Fondufe-Mittendorf.
Presenter affiliation: University of Kentucky, Lexington, Kentucky. 6

REGULATION OF HYPOXIA-INDUCIBLE FACTOR STABILITY AND ACTIVATION BY TANKYRASES

Esteban Zamudio-Martínez, Daniel Delgado-Bellido, Ángel García-Díaz, Jose M Rodríguez-Vargas, Javier Oliver-Pozo

Instituto de Parasitología y Biomedicina López Neyra, CSIC and CIBERONC, Instituto Salud Carlos III, Cellular Biology and Immunology, Granada, Spain

Tankyrase 1 (TNKS1) and tankyrase 2 (TNKS2) are two proteins that have been linked to different cellular functions including telomere elongation, mitotic progression and Wnt signaling. Furthermore, altered levels of TNKS1 and/or TNKS2 expression have been reported in several types of cancer such as colon, lung or brain. Tankyrases are well-known by the synthesis of linear chains of poly(ADP-ribose) (PAR) to produce posttranslational modifications onto their target proteins. Tumor hypoxia is one of the main problems related to the increased aggressiveness and therapeutic resistance in most cancers. The adaptation to this situation is carried out by the heterodimeric transcription factors hypoxia-inducible factor (HIF). In particular, the oxygen-dependent proteins HIF-1α/HIF-2α and the constitutively expressed protein HIF-1β are responsible for the induction of genes that allow the adaptation and survival of cells to hypoxia. PARylation by TNKS is tightly linked to ubiquitination by the ubiquitin E3 ligase RNF146 in order to maintain protein stability via proteasomal degradation. However, some authors think that the importance of tankyrase is sometimes associated only to the binding of tankyrases instead of the PARylation of their targets. In view of the importance that tankyrases are acquiring as molecular targets for cancer treatment, we aimed to elucidate the implication of TNKS in the regulation of HIF-1α turnover and function in different tumor settings. Our results suggest that there is a connection between tankyrases and HIF-1α stability. The use of TNKS1/2 inhibitors XAV939 and G007-LK does not seem to affect the stability of HIF-1α, although TNKS1 and TNKS1/2 silencing (but not TNKS2 alone) results in HIF-1α decreased stability and defective transcriptional activation. The silencing of RNF146 neither affects to HIF-1α stability, pointing out the relevancy of TNKS1/2 presence instead of their capability of PARylation in the tumor adaptation to hypoxic situations. Immunoprecipitation and immunofluorescence results also hint at the formation of a complex between TNKS1/2 and HIF-1α. Tankyrase substrates are characterized by the presence of one or more Tankyrase Binding Motifs (TBMs) that mediate the interaction with the ankyrin domain of TNKS1/2. The amino acid sequence of HIF-1α contains a possible TBM. We carried out a site-directed mutagenesis within the TBM present in HIF-1α and the experiments are on their way to corroborate whether this motif mediates the binding to tankyrases.
In conclusion, TNKS1/2 interact and modulate HIF-1α stability and activation and given the pivotal role of both proteins in tumor development, TNKS inhibitors might have a large potential in multiple tumor types with hypoxic traits.