UBIQUITIN-BASED REGULATION OF GENOME STABILITY

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SUMMARY & MISSION STATEMENT

Ubiquitin conjugation is a widely-used protein modification that regulates many cellular pathways relevant for cancer cell proliferation and genome integrity. The ubiquitin system entails several enzymatic – and therefore "druggable" – activities that drive ubiquitination to specific proteins. Targeting specific ubiquitinating enzymes that modulate cancer-relevant pathways is thus an intensively explored strategy for next generation anticancer therapies. As various approved anticancer drugs interfere with DNA damage response and DNA replication, inactivation of regulatory ubiquitin modifications in the stress response is a promising strategy to potentiate chemotherapy.
Our goal is to expand the mechanistic understanding of the ubiquitin-mediated control of the DNA damage response and DNA replication processes when cells are challenged by harmful conditions, such as genotoxic stress, inflammation, pathogen infection.

OVERVIEW

Ubiquitination of chromatin and chromatin-associated factors is a key step to activate the DNA repair pathways triggered by DNA damage and to promote accurate DNA replication, thereby ensuring genome stability. We are interested in further elucidating the molecular basis underlying the DNA repair pathway choice between homologous recombination (HR), mediated by BRCA1, and non-homologous end-joining (NHEJ), mediated by 53BP1, and how these events impact on genome integrity. Moreover, we aim to understand how these mechanisms regulating genome integrity are modulated in specific cellular contexts – i.e. inflammation – thereby providing additional insights into inflammation-induced cancer development.

SELECTED CANCER RELATED PUBLICATIONS

Histone ubiquitination by the DNA damage response is required for efficient DNA replication in unperturbed S-phase. Schmid JA, Berti M, Walser F, Raso MC, Schmid F, Krietsch J, Stoy H, Zwicky K, Ursich S, Freire R, Lopes M and Penengo L. **Molecular Cell**, under second revision after peer review.

ASH1L histone methyltransferase stimulates global-genome nucleotide excision repair. Balbo Pogliano C, Gatti M, Rüthemann P, Garajovà Z, Penengo L, Naegeli H. **Nat Commun**. 2017;8: 1333.

Replication fork slowing and reversal upon genotoxic stress require PCNA polyubiquitination and ZRANB3 DNA translocase activity. Vujanovic M, Terraneo N, Zellweger R, Raso MR, Schmid JA, Taglialatela A, Holland CL, Zwicky K, Herrador R, Jacobs H, Cortez D, Ciccia A, Penengo L and Lopes M. **Molecular Cell**. 2017;67: 882-890.

A novel BRCA1-associated protein-1 isoform affects response of mesothelioma cells to drugs impairing BRCA1-mediated DNA repair. Parrotta R, Okonska A, Ronner M, Weder W, Stahel R, Penengo L, Felley-Bosco E. **Journal of thoracic oncology** 2017;S1556-0864(17)30274-5.

RNF168 promotes non-canonical K27 ubiquitination to signal DNA damage. Gatti M, Pinato S, Maiolica A, Rocchio F, Prato MG, Aebersold R and Penengo L. **Cell Reports**. 2015;10: 226-238.

A novel ubiquitin mark at the N-terminal tail of histone H2As targeted by RNF168 ubiquitin ligase. Gatti M, Pinato S, Maspero E, Soffientini P, Polo S and Penengo L. **Cell Cycle** 2012;11: 2538-2544.

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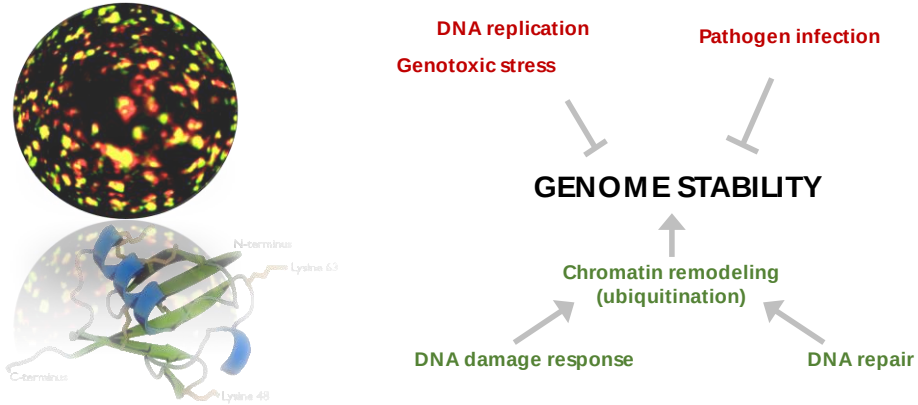

modifications, such as phosphorylation and the ubiquitination (visualized using specific markers, left part of the picture), is essential to activate the DNA damage response and the DNA repair pathways.