CENTRO DE INVESTIGACIÓN DEL CÁNCER

Instituto de Biología Molecular y Celular del Cáncer (IBMCC)

VNiVERSiDAD D SALAMANCA

CSIC

Centro de Investigación del Cáncer
Instituto de Biología Molecular y Celular del Cáncer
Universidad de Salamanca – CSIC
Campus Miguel de Unamuno
37007, Salamanca
España

Tel.: 923 294720
Fax: 923 294743

www.cicancer.org

New study explains how the tolerance to DNA damage pathway is down-regulated during DNA synthesis at replication forks.

- The research, developed by the team led by Avelino Bueno at Cancer Research Center (CIC-IBMCC) and researchers at Center for Biological Research (CIB-CSIC), has been published in ***Cell Reports***.

- PCNA deubiquitylation is a key mechanism for modulation of lesion bypass during replication. Our data suggest that damage tolerance is modulated at replication forks to limit the extension of bypass events and sustain a processive and efficient replication of DNA.

DNA damage is a major source of genome instability and cancer in living cells. To deal with DNA damage, cells have evolved three major pathways that are conserved among organisms: checkpoint response, repair mechanisms and tolerance to DNA damage. The DNA damage tolerance pathway plays a key role in protecting cell viability through translesion synthesis and template switching-mediated bypass of genotoxic DNA-polymerase-blocking base lesions. Both tolerance branches critically rely on ubiquitylation of the proliferating-cell nuclear antigen (PCNA) on lysine 164. Although the evolutionary conserved mechanism of PCNA ubiquitylation is well understood, the deubiquitylation of PCNA have remained largely uncharacterized until now. In recent years, our group have contributed to the molecular characterization of the principal components involved in this process in two model systems. In this new publication, we report that budding yeast Ubp10 and Ubp12 ubiquitin proteases cooperate in PCNA deubiquitylation when associated to replication forks as functional components of the replisome. Interestingly, Ubp10 and Ubp12 downregulate translesion DNA polymerases recruitment and template switch events engaging nascent strands, revealing that PCNA deubiquitylation is a key mechanism for modulation of lesion bypass during replication.

Álvarez, V., Frattini, C., Sacristán, M., Gallego-Sánchez, A., Bermejo, R. and Bueno, A. (2019). PCNA Deubiquitylases Control DNA Damage Bypass at Replication Forks. ***Cell Reports*** 29: 1-13. doi: 10.1016/j.celrep.2019.09.054

https://www.cell.com/cell-reports/fulltext/S2211-1247(19)31242-2#secsectitle0025