Deregulated levels of RUVBL1 induce transcription-dependent replication stress

Rossitsa H. Hristova [1], Stoyno S. Stoynov [1], Irina R. Tsaneva [2], Anastas G. Gospodinov [1]

1. Roumen Tsanev Institute of Molecular Biology, Bulgarian Academy of Sciences, Acad. G. Bonchev Str. 21, 1113, Sofia, Bulgaria

2.Department of Biochemistry and Molecular Biology, University College London, London WC1E 6BT, UK

Chromatin regulators control transcription and replication, however if and how they might influence the coordination of these processes still is largely unknown. RUVBL1 and the related ATPase RUVBL2 participate in multiple nuclear processes and are implicated in cancer. Here, we report that both the excess and the deficit of the chromatin regulator RUVBL1 impede DNA replication as a consequence of altered transcription. Surprisingly, cells that either overexpressed or were silenced for RUVBL1 had slower replication fork rates and accumulated phosphorylated H2AX, dependent on active transcription. However, the mechanisms of transcription-dependent replication stress were different when RUVBL1 was overexpressed and when depleted. RUVBL1 overexpression led to increased c-Myc-dependent pause release of RNAPII, as evidenced by higher overall transcription, much stronger Ser2 phosphorylation of Rpb1- C-terminal domain, and enhanced colocalization of Rpb1 and c-Myc. RUVBL1 deficiency resulted in increased ubiquitination of Rpb1 and reduced mobility of an RNAP subunit, suggesting accumulation of stalled RNAPIIs on chromatin. Overall, our data show that by modulating the state of RNAPII complexes, RUVBL1 deregulation induces replication-transcription interference and compromises genome integrity during S-phase.