



Eleni Petsalaki

University of Crete
Greece

A novel mechanism for chromatin bridge sensing by the abscission checkpoint in human cells

Abstract:

Chromatin bridges are DNA strings that link anaphase poles or daughter nuclei and are associated with carcinogenesis. DNA bridges occur from the separation of twisted, linked chromatin that is caused by problems in DNA replication or incomplete DNA decatenation. In response to chromatin bridges, cells delay abscission by activating the abscission checkpoint which delays completion of cytokinesis in order to prevent chromatin breakage or tetraploidization by furrow regression. Here, we show that spontaneous or replication stress-induced chromatin bridges derived from catenated DNA exhibit “knots” of tangled, overtwisted DNA next to the midbody. Topoisomerase II α (Top2 α), an enzyme that relaxes supercoils and untangles catenated DNA forms irreversible Top2-DNA cleavage complexes (Top2ccs) on DNA knots. Inhibition of Top2 α results in diminished localization of Rad17, MRN, ATM, Chk2 and CPC complex to the DNA bridges and induces chromatin bridge breakage. Furthermore, proteolytic degradation of Top2ccs is required for localization of Rad17 to the bridge DNA. In turn, Rad17 promotes recruitment of the MRN complex to DNA knots and downstream abscission checkpoint signaling to delay abscission and prevent chromatin bridge breakage in cytokinesis. In contrast, chromatin bridges generated by dicentric chromosomes do not exhibit DNA knots or Top2ccs next to the midbody, and fail to recruit Top2 α , Rad17 and other downstream proteins and are unable to induce an abscission delay. Our results describe a novel mechanism by which the abscission checkpoint detects chromatin bridges in human cells, through generation of irreversible Top2ccs on DNA knots. Because chromosomal instability is a major cause of cancer, identifying new genes that protect genome integrity is very important for cancer research.

Biography

Eleni Petsalaki is a Post Doctoral Research Scientist in Dr George Zachos' lab at University of Crete, Greece. She completed her PhD in 2014 in Molecular Biology and Biomedicine at the Department of Biology. Her main interest is mitotic cell division and mechanisms that monitor mitotic progression called the mitotic spindle checkpoint and the abscission checkpoint. She is an author of 16 publications including Journal of Cell Biology, Nature Communications, Journal of Cell Science and others. Her publications have received 305 citations so far. She is currently a member of FEBS, AACR, and Royal Society of Biology.