Novel Replication Fork Protection Factor

Zadorozhny, Karina (School: První české gymnázium v Karlových Varech)

Replication stress is one of the major sources of genomic instability in tumor cells. DNA replication is threatened by various obstacles which impede its progression and can lead to nascent DNA degradation and fork collapse. An absence of RAD51AP1 protein leads to replication fork slowdown and causes an extensive replication stress, however, the mechanism by which RAD51AP1 participates in DNA replication remains unknown. This work reports a previously unknown role of RAD51AP1 in DNA protection as revealed by reconstitution of replication fork degradation in vitro using synthetic DNA substrates. Strikingly, recombinant RAD51AP1 bound to replication forks is specifically protecting DNA against degradation by an MRE11 exonuclease. Moreover, RAD51AP1 acts synergistically with its interaction partner RAD51. Analysis of the stability and conformation of DNA-protein complexes provided also a mechanistic understanding of DNA protection – while RAD51 prevents DNA degradation by forming helical filaments and coating DNA, RAD51AP1 preferentially binds to ss/dsDNA junctions and blocks its accessibility for nucleolytic cleavage. Altogether, these results uncover a novel role of RAD51AP1 in the maintenance of genome integrity by stabilization of stalled replication forks. This is especially important in the context of the elevated level of replication stress in cancer cells and presented work can provide an explanation of why RAD51AP1 is frequently mutated in a variety of tumors.

Awards Won:

Third Award of $1,000