Abstract

DNA replication is the most vulnerable process of DNA metabolism in proliferating cells and therefore it is tightly controlled and coordinated with processes that maintain genomic stability. Human RecQ helicases are among the most important factors involved in the maintenance of replication fork integrity, especially under conditions of replication stress. Collisions between replication and transcription machineries represent a significant source of genomic instability. RECQ5 DNA helicase binds to RNA-polymerase (RNAP) II during transcription elongation and suppresses transcription-associated genomic instability. Here we show that RECQ5 also associates with RNAPI and enforces the stability of ribosomal DNA arrays in cells exposed to replication stress. We demonstrate that RECQ5 associates with transcription complexes in DNA replication foci and counteracts replication fork stalling in RNAPI- and RNAPII-transcribed genes, suggesting that RECQ5 exerts its genome stabilizing effect by acting at sites of concomitant replication and transcription. Moreover, RECQ5-deficient cells accumulate RAD51 foci that are formed in a BRCA1-dependent manner at sites of interference between replication and transcription and likely represent unresolved replication intermediates. Importantly, BRCA1-dependent formation of RAD51 foci at these sites requires active transcription. Further, we provide evidence that RECQ5 promotes RAD18-dependent PCNA ubiquitination at sites of replication-transcription interference by its interaction with PCNA. This is also manifested by the accumulation of RAD18 foci in the absence of RECQ5 or the presence of a RECQ5 mutant defective in PCNA binding. The helicase activity of RECQ5 promotes unloading of ubiquitinated PCNA from chromatin and counteracts the accumulation of RAD51 foci in S-phase cells. These findings suggest that RECQ5 promotes PCNA remodeling at replication forks stalled due to the collision with transcription complex and in coordination with BRCA1-mediated replication fork stabilization promotes the resolution of replication-transcription collisions.