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RNA-mediated genome instability and transcription-replication conflicts

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Genome instability is a hallmark of cancer cells. As a cell pathology is frequently associated with mutations in factors involved in the DNA damage response (DDR), including DNA replication, repair and recombination. However, different studies have revealed that RNA and transcription can be a natural source of genome instability, both in the absence and upon the action of exogenous genotoxic agents. In most cases this is due to transcription-replication conflicts that are stimulated by co-transcriptional R-loops that if not properly resolved lead to replication fork breakage. We try to define the mechanisms controlling these processes by focusing on two type of factors: RNA metabolic factors and chromatin remodelers and modifiers. We have shown that a number of such factors, including the UAP56/DDX39B, DDX47 and DDX5 RNA helicases, and the SWI/SNF, FACT and SIN3A chromatin remodeler and modifier complexes, are key in preventing or resolving R-loops and their associated transcription-replication conflicts. Interestingly, our recent results indicate that the apparent redundancy of factors controlling the causes of the conflicts and R-loops is in part due to cell cycle phase dependency and a mediator role facilitating the action of DDR factors at stalled replication forks. We will discuss the biological meaning of our new results and their relation with mutagenesis.

Keywords:
Genetic instability; R-loops; Transcription-Replication conflicts; Chromatin; DSB repair, Mutagenesis.