ID de Contribution: **47** Type: **Non spécifié**

Recombination-transcription conflicts: from DNA joint molecule metabolism to repair outcome

Homologous recombination is a template-dependent DNA double-strand break repair mechanism. A key step of HR is DNA strand invasion, which consists of the pairing of the single-stranded DNA flanking the break site to a complementary strand in a homologous double-stranded DNA (dsDNA) leading to the formation of a DNA joint molecule called a D-loop. D-loop metabolism is likely central in the donor selection process, regulated by various conserved trans-acting factors involved in genome maintenance, such as the Mph1FANCM and Srs2FBH1 helicases, as well as the Sgs1-Top3-Rmi1BLM-TOPO3⊠-RMI1/2 complex. However, little is known about the role of transcription, a ubiquitous and presumably competing cis-acting DNA-dependent event, on the core steps of homologous recombination. The goal of my project is to investigate the potential conflicts between recombination and transcription and their consequences for genome stability in S. cerevisiae. To this end, we used an assay for D-loop quantification and initiation of DNA synthesis at an ectopic donor site whose transcription can be modulated at will. We show that colinear transcription is the main cause of nascent D-loop disruption, and acts independently of the aforementioned trans disruption activities. This effect is acute, as inducing donor transcription for a few minutes prior to sample collection recapitulates D-loop inhibition by strong constitutive promoters. Moreover, it inhibits the initiation of DNA synthesis. Finally, transcription lowers the frequency of multi-invasions-induced rearrangements. These preliminary results suggest that the act of transcription represents a potent anti-recombination mechanism unevenly protecting the genome against rearrangements.

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