Genomic instability at the crossroads of replication and transcription

Venue: Cluster seminar hall 2

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Abstract

Conflicts between DNA replication and transcription are inevitable, as both processes concurrently use the same DNA template, especially in rapidly diving bacterial and cancer cells resulting in collisions between their machineries. Replication-transcription collisions are known to threaten genomic stability and underlie diseases. However, the nature, mechanisms and impact of collision-induced mutations remain unknown. We developed an unbiased mutation assay in bacteria and revealed that collisions generate two major mutations: insertions/deletions (indels) and promoter base substitutions. We found that indels were enriched at the vicinity where the replication fork first encounters a transcription complex, suggesting that collisions trigger indels by impeding replication. The second mutation signature was a highly deleterious mutation hotspot in the promoter, created by a novel mechanism of adenine deamination, as a result of collisions interfering with transcription initiation. Thus, replication and transcription antagonize each other during conflicts, resulting in deleterious mutations via distinct mechanisms. Altogether, as these mutation signatures are widespread, we conclude that replication-transcription collisions are fundamental source of spontaneous mutations across domains of life. My future research aims at illuminating the mechanisms of replication-transcription collisions, to address the everlasting problem of multi-drug resistance in bacteria and define novel targets for drug discovery. Further, I would like to apply the basic biology of collision-induced mutagenesis in protein engineering & biotechnology for applications in health and industry.