Mechanisms that modulate replication fork stability and R-loop accumulation during the conflict with transcription

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Project

DNA replication and transcription are processes that can interfere with each other leading to endogenous DNA damage, which a major cause of genomic instability in cancer and other degenerative diseases. Head-on replication-transcription collisions are particularly detrimental for genome integrity maintenance, because they promote the accumulation of highly recombinogenic and mutagenic structures called R-loops (Brambati et al., 2020).
We showed that the budding yeast Sen1 helicase, the ortholog of human Senataxin mutated in cancer and AOA2/ALS4 neurological diseases, favors fork progression across transcribed genes, preventing R-loop accumulation (Alzu et al., 2012). In the absence of Sen1, transcription becomes and impenetrable barrier to fork advancing head-on, requiring specific rescue mechanisms that prevent fork breakage and terminate DNA replication (Brambati et al., 2018).
Our approach is to use genetic and genomic techniques combined with molecular biology methods, including the analysis of the replication intermediates by 2D gel technique (Zardoni et al., 2020), to explore the mechanisms and factors that preserve the integrity of fork colliding with transcription and the pathological transitions occurring at forks arrested by transcription in the absence of Sen1 and other anti-R-loop proteins.

References

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