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The accurate transmission of the genetic material requires a faithful replication of the chromosomes and their equal segregation to the progeny. The perturbation of the dynamic of DNA replication, known as replication stress, has emerged as a major source of genome instability contributing to the early stages of carcinogenesis.

The causes of replication stress are many and varied, but they ultimately affect the progression of replication forks and can jeopardize the even segregation of chromosome in mitosis. The aim of our research is to decipher the molecular transactions occurring at replication forks in response to replication stress and to understand how these mechanisms trigger genome instability. In particular, the team focuses on the mechanisms of homologous recombination, a well evolutionary conserved pathway, known to prevent genome instability and tumour development in humans. Such questions are important to address in basic cancer research to understand how genetic instability arises from replication stress and contributes to cancer devolvement or genomic disorders.

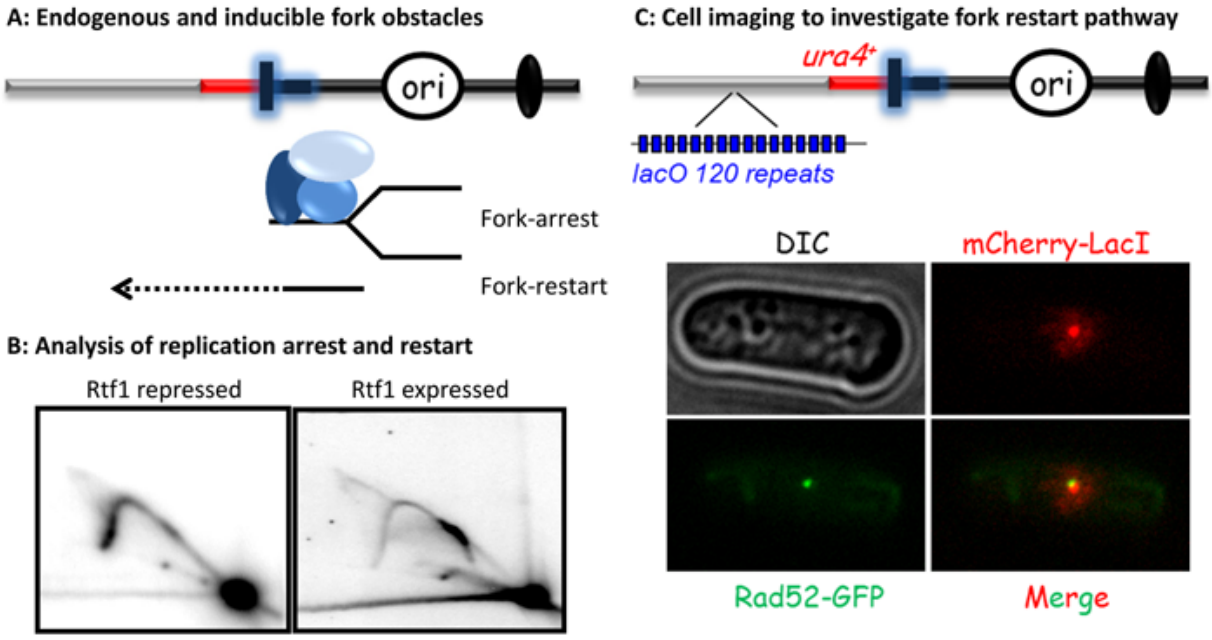

Figure 1: Cellular model to induce endogenous replication stress at targeted locus. (A) A natural fork obstacle is exploited in fission yeast to induce endogenous replication stress at a targeted locus. The protein Rtf1 which expression is regulated, binds a specific sequence (in blue) and mediates fork arrest. Replication arrest and restart are investigated by combining molecular (B) and cellular biology (C).

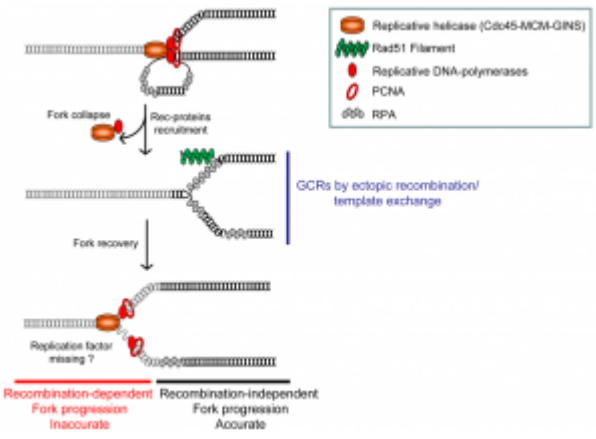

Figure 2: Model of replication stress-induced genetic instability at collapsed forks.

To investigate the causes and the consequences of replication stress, the yeast *Schizossacharomyces pombe* is a powerful model system amendable to genetic, cellular and molecular biology, thus allowing us to manipulate and create endogenous replication stress (Fig 1). Our team has identified that homologous recombination is an efficient pathway to restart replication forks, but that this comes at the expense of potential genetic instability, including tumour-like genome rearrangements (genomic deletion/translocations). Also, we have reported that replication restart by homologous recombination results in the progression of an error-prone replication fork, liable to replication slippage (Fig 2). Finally, we have identified that the DNA Damage Response is involved in regulating the extent of genetics errors

committed during replication restart by homologous recombination.

By combining genetics screens, cell imaging and molecular biology, the team focuses on deciphering the replication maintenance functions of homologous recombination, from fork-restart to fork-protection functions. As molecular transactions at blocked replication forks occur in a chromatin context, the team has also investigated the links between chromatin assembly pathways and the fidelity of homologous recombination. We have identified CAF-1 as a novel factor that challenges the fidelity of replication restart by homologous recombination.

Key publications

Year of publication 2017

Ana Teixeira-Silva, Anissia Ait Saada, Julien Hardy, Ismail Iraqui, Marina Charlotte Nocente, Karine Fréon, Sarah A E Lambert (2017 Dec 7)
The end-joining factor Ku acts in the end-resection of double strand break-free arrested replication forks.
Nature communications : 1982 : DOI : 10.1038/s41467-017-02144-5

Anissia Ait Saada, Ana Teixeira-Silva, Ismail Iraqui, Audrey Costes, Julien Hardy, Giulia Paoletti, Karine Fréon, Sarah A E Lambert (2017 May 4)
Unprotected Replication Forks Are Converted into Mitotic Sister Chromatid Bridges.
Molecular cell : 398-410.e4 : DOI : 10.1016/j.molcel.2017.04.002

Year of publication 2016

Simon Gemble, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Denis Biard, Sarah Lambert, Mounira Amor-Guéret (2016 Aug 15)
A balanced pyrimidine pool is required for optimal Chk1 activation to prevent ultrafine anaphase bridge formation.
Journal of cell science : 3167-77 : DOI : 10.1242/jcs.187781

Year of publication 2015

Simon Gemble, Akshay Ahuja, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Julien Dairou, Denis S F Biard, Sarah Lambert, Massimo Lopes, Mounira Amor-Guéret (2015 Jul 16)
Pyrimidine Pool Disequilibrium Induced by a Cytidine Deaminase Deficiency Inhibits PARP-1 Activity, Leading to the Under Replication of DNA.
PLoS genetics : e1005384 : DOI : 10.1371/journal.pgen.1005384

Year of publication 2014

Violena Pietrobon, Karine Fréon, Julien Hardy, Audrey Costes, Ismail Iraqui, Françoise Ochsenbein, Sarah A E Lambert (2014 Oct 14)
The chromatin assembly factor 1 promotes Rad51-dependent template switches at replication forks by counteracting D-loop disassembly by the RecQ-type helicase Rqh1.
PLoS biology : e1001968 : DOI : 10.1371/journal.pbio.1001968

Ellen Tsang, Izumi Miyabe, Ismail Iraqui, Jiping Zheng, Sarah A E Lambert, Antony M Carr (2014 Jul 1)
The extent of error-prone replication restart by homologous recombination is controlled by Exo1 and checkpoint proteins.
Journal of cell science : 2983-94 : DOI : 10.1242/jcs.152678