

POSTER PRESENTATION

Open Access

# Global control of DNA replication timing by the budding yeast telomere protein Rif1

Laure Lemmens<sup>1</sup>, Stefano Mattarocci<sup>1</sup>, Isabella Marcomini<sup>1</sup>, Tianlai Shi<sup>2</sup>, Cindy Follonier<sup>3</sup>, Massimo Lopes<sup>3</sup>, Nicolas Thomä<sup>2</sup>, David Shore<sup>1\*</sup>

From Epigenetics and Chromatin: Interactions and processes  
Boston, MA, USA. 11-13 March 2013

## Background

DNA replication in eukaryotes is initiated from specific chromosomal sites (origins) that fire in a defined, cell type-specific temporal pattern. This replication program appears to be under epigenetic control through mechanisms that are still poorly understood.

## Materials and methods

Studies were done in *Saccharomyces cerevisiae* (W303 background) using standard genetic and molecular methods. Chromatin immunoprecipitation assays were performed in strains in which genes encoding DNA polymerase 1 or 2 were epitope-tagged at their endogenous loci.

## Results

We showed previously that telomere TG-repeat tract length exerts an epigenetic effect in *cis* on the activity of nearby subtelomeric replication origins, such that a shortened telomere will replicate earlier [1]. Here we show that deletion of the *RIF1* gene, which encodes a telomere-specific Rap1-interacting protein involved in telomere length regulation and telomere “capping” [2-5], also leads to premature replication of two different subtelomeric regions examined. A similar effect of *RIF1* deletion on other subtelomeric regions has recently been described [6]. We show here that the effect of *RIF1* deletion is epistatic to loss of Tel1 or Mec1 (ATM and ATR kinases), does not affect the intra-S phase checkpoint, and operates through a different pathway than the silencing protein Sir3. Deletion of a normally dormant telomere-proximal replication origin exerts a similar effect on replication timing as does deletion of

*RIF1*, and these two effects are additive. Strikingly, deletion of *RIF1* partially suppresses temperature-sensitive mutations in a number of essential genes that encode regulators of DNA replication initiation, without affecting the levels of the relevant gene products, several of which are present in limiting amounts.

## Conclusions

The budding yeast telomere-binding protein Rif1 is shown here to be a global regulator of DNA replication initiation whose loss leads to precocious replication of subtelomeric domains in the budding yeast. This appears to be a highly conserved function of Rif1, since its homologs have recently been shown to exert related effects in both fission yeast and mammalian cells [7-9]. Experiments will be described aimed at understanding the mechanistic basis of the effect of Rif1 on replication timing.

## Author details

<sup>1</sup>NCCR “Frontiers in Genetics” program and Department of Molecular Biology, University of Geneva, Geneva 4, CH-1211, Switzerland. <sup>2</sup>Friedrich Miescher Institute for Biomedical Research, Basel, CH-4058, Switzerland. <sup>3</sup>Institute of Molecular Cancer Research, University of Zurich, Zurich, CH-8057, Switzerland.

Published: 18 March 2013

## References

1. Bianchi A, Shore D: Early replication of short telomeres in budding yeast. *Cell* 2007, **128**:1051-1062.
2. Hardy CFJ, Sussel L, Shore D: A RAP1-interacting protein involved in silencing and telomere length regulation. *Genes Dev* 1992, **6**:801-814.
3. Ribeyre C, Shore D: Anticheckpoint pathways at telomeres in yeast. *Nature structural & molecular biology* 2012, **19**:307-313.
4. Anbalagan S, Bonetti D, Lucchini G, Longhese MP: Rif1 supports the function of the CST complex in yeast telomere capping. *PLoS genetics* 2011, **7**:e1002024.
5. Xue Y, Rushton MD, Maringele L: A novel checkpoint and RPA inhibitory pathway regulated by Rif1. *PLoS genetics* 2011, **7**:e1002417.
6. Lian HY, Robertson ED, Hiraga S, Alvino GM, Collingwood D, McCune HJ, Sridhar A, Brewer BJ, Raghuraman MK, Donaldson AD: The effect of Ku on

<sup>1</sup>NCCR “Frontiers in Genetics” program and Department of Molecular Biology, University of Geneva, Geneva 4, CH-1211, Switzerland  
Full list of author information is available at the end of the article

telomere replication time is mediated by telomere length but is independent of histone tail acetylation. *Molecular biology of the cell* 2011, **22**:1753-1765.

7. Yamazaki S, Ishii A, Kanoh Y, Oda M, Nishito Y, Masai H: **Rif1 regulates the replication timing domains on the human genome.** *The EMBO journal* 2012, **31**:3667-3677.
8. Hayano M, Kanoh Y, Matsumoto S, Renard-Guillet C, Shirahige K, Masai H: **Rif1 is a global regulator of timing of replication origin firing in fission yeast.** *Genes & development* 2012, **26**:137-150.
9. Cornacchia D, Dileep V, Quivy JP, Foti R, Tili F, Santarella-Mellwig R, Antony C, Almouzni G, Gilbert DM, Buonomo SB: **Mouse Rif1 is a key regulator of the replication-timing programme in mammalian cells.** *The EMBO journal* 2012, **31**:3678-3690.

doi:10.1186/1756-8935-6-S1-P99

**Cite this article as:** Lemmens *et al.*: Global control of DNA replication timing by the budding yeast telomere protein Rif1. *Epigenetics & Chromatin* 2013 **6**(Suppl 1):P99.

**Submit your next manuscript to BioMed Central  
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

