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TRF1 suppresses break induced replication and early onset of ALT induction

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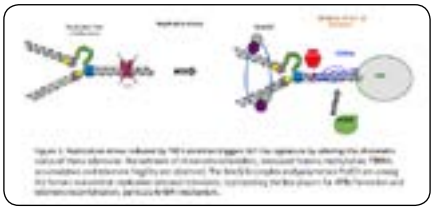
Persistent during DNA replication or inappropriately processed, telomere DNA secondary structures can have pathological consequences and are an established source of genome instability. Despite the advances on the role of DNA helicases and shelterin proteins facilitating replication through telomeric secondary structures, the step-by-step analysis of induction of telomere fragility remain poorly understood. TRF1 is a key factor in facilitating replication at telomeres and we took advantage of its function to study the events happening at telomeres using an unbiased proteomic approach. Proteomic of isolated chromatin revealed that telomeric chromatin of TRF1 deficient cells resemble ALT telomeres with the recruitment of PML and also the enrichment of many ALT specific factors including ATRX, SMC5/6 complex. We also report for the first time that the high levels of recombination detected by CO-FISH in TRF1-/- cells is dependent on SMC5 and is in fact a conservative dependent DNA synthesis mediated by BIR and POLD3. Notably, we could not detect all hallmarks of ALT positive cells in our experimental system, including no heterogeneous telomere length and no c-circle formation. Telomere fragility and common fragile site share at least a common trigger, which is replication hindrance, both induced by aphidicolin treatment. Despite POLD3 dependent BIR being involved in CFS expression and now observed in our study at TRF1 depleted telomeres, we claim that this conservative DNA synthesis mechanism is not responsible for the induction of telomere fragility in TRF1 deficient cells. Therefore, all indicate that the mechanism generating telomere fragility and CFS are different.



Recent Publications

1. León Ortiz A M, Panier S, Sarek G, Vannier J B and Boulton S J (2018) A distinct class of genome rearrangements driven by illegitimate recombination. Mol Cell. 69(2):292-305.e6.
2. Speckmann C, Sahoo S S, Rizzi M, Hirabayashi S, Karow A, Serwas N K, Hoemberg M, Damatova N, Schindler D, Vannier J B, Boulton S J, Pannicke U, Göhring G, Thomay K, Verdu Amoros J J, Hauch H, Woessmann W, Escherich G, Laack E, Rindle L, Seidl M, Rensing Ehl A, Lausch E, Jandrasits C, Strahm B, Schwarz K, Ehl S R, Niemeyer C, Boztug K and Wlodarski M W (2017) Clinical and molecular heterogeneity of RTEL1 deficiency. Front Immunol. 8:449.
3. Sarek G, Vannier J B, Panier S, Petrini J H and Boulton S J (2015) TRF2 recruits RTEL1 to telomeres in S phase to promote T-loop unwinding. Mol Cell 57(4):622–635.
4. Vannier J B, Sarek G and Boulton S J (2014) RTEL1: functions of a disease-associated helicase. Trends in Cell Biology 24(7):416-25.
5. Vannier J B, Sandhu S, Petalcorin M I, Wu X, Nabi Z, Ding H and Boulton S J (2013). RTEL1 is a replisome-associated helicase that promotes telomere and genome-wide replication. Science 342(6155):239–242.

Biography

Jean Baptiste Vannier has developed his expertise in telomere homeostasis during his Doctoral studies, in the laboratory of Dr. Charles White, where he implicated several different DNA damage proteins in protecting uncapped telomeres from unscheduled recombination in plant model *Arabidopsis thaliana* (Vannier *et al., EMBO J,* 2006; *Plos Gen.,* 2009). During his Postdoctoral research with Dr. Simon Boulton, he established the mechanistic basis of RTEL1 DNA helicase function at mammalian telomeres in T-loop disassembly and provided insight into the source and prevention of telomere fragility (Vannier *et al., Cell,* 2012; *Science,* 2013). His group uses epigenetic and chromatin DNA-related methodologies to investigate the cellular response to replication stress and the enzymatic activities that result in telomere replication aberrations. This represents an outstanding challenge that will provide a novel framework for understanding the contributions of replication factors in general DNA replication, genome stability and cancer.