Publications de l’équipe
Télomères et Cancer

Année de publication : 2018


**Human RTEL1 stabilizes long G-overhangs allowing telomerase-dependent over-extension**
*Nucleic Acids Research*: DOI : 10.1093/nar/gky173

**Résumé**

Telomere maintenance protects the cell against genome instability and senescence. Accelerated telomere attrition is a characteristic of premature aging syndromes including Dyskeratosis congenita (DC). Mutations in hRTEL1 are associated with a severe form of DC called Hoyeraal-Hreidarsson syndrome (HHS). HHS patients carry short telomeres and HHS cells display telomere damage. Here we investigated how hRTEL1 contributes to telomere maintenance in human primary as well as tumor cells. Transient depletion of hRTEL1 resulted in rapid telomere shortening only in the context of telomerase-positive cells with very long telomeres and high levels of telomerase. The effect of hRTEL1 on telomere length is telomerase dependent without impacting telomerase biogenesis or targeting of the enzyme to telomeres. Instead, RTEL1 depletion led to a decrease in both G-overhang content and POT1 association with telomeres with limited telomere uncapping. Strikingly, overexpression of POT1 restored telomere length but not the overhang, demonstrating that G-overhang loss is the primary defect caused by RTEL1 depletion. We propose that hRTEL1 contributes to the maintenance of long telomeres by preserving long G-overhangs, thereby facilitating POT1 binding and elongation by telomerase.

Année de publication : 2017


**ZBTB48 is both a vertebrate telomere-binding protein and a transcriptional activator**
*EMBO Report*: DOI : 10.15252/embr.201744095

**Résumé**

Telomeres constitute the ends of linear chromosomes and together with the shelterin complex form a structure essential for genome maintenance and stability. In addition to the constitutive binding of the shelterin complex, other direct, yet more transient interactions are mediated by the CST complex and HOT1/HMBOX1, while subtelomeric variant repeats are recognized by NR2C/F transcription factors. Recently, the Kruppel-like zinc finger protein ZBTB48/HKR3/TZAP has been described as a novel telomere-associated factor in the vertebrate lineage. Here, we show that ZBTB48 binds directly both to telomeric and to subtelomeric variant repeat sequences. ZBTB48 is found at telomeres of human cancer cells regardless of the mode of telomere maintenance and it acts as a negative regulator of
telomere length. In addition to its telomeric function, we demonstrate through a combination of RNAseq, ChIPseq and expression proteomics experiments that ZBTB48 acts as a transcriptional activator on a small set of target genes, including mitochondrial fission process 1 (MTFP1). This discovery places ZBTB48 at the interface of telomere length regulation, transcriptional control and mitochondrial metabolism.

Bruno Teste, Jerome Champ, Arturo Londono-Vallejo, Stéphanie Descroix, Laurent Malaquin, Jean-Louis Viovy, Irena Draskovic, Guillaume Mottet (2017 Jan 17)

Chromatin immunoprecipitation in microfluidic droplets: towards fast and cheap analyses.

Lab on a chip : 530-537 : DOI : 10.1039/c6lc01535b

Résumé

Genetic organization is governed by the interaction of DNA with histone proteins, and differential modifications of these proteins is a fundamental mechanism of gene regulation. Histone modifications are primarily studied through chromatin immunoprecipitation (ChIP) assays, however conventional ChIP procedures are time consuming, laborious and require a large number of cells. Here we report for the first time the development of ChIP in droplets based on a microfluidic platform combining nanoliter droplets, magnetic beads (MB) and magnetic tweezers (MT). The droplet approach enabled compartmentalization and improved mixing, while reducing the consumption of samples and reagents in an integrated workflow. Anti-histone antibodies grafted to MB were used as a solid support to capture and transfer the target chromatin from droplets to droplets in order to perform chromatin immunoprecipitation, washing, elution and purification of DNA. We designed a new ChIP protocol to investigate four different types of modified histones with known roles in gene activation or repression. We evaluated the performances of this new ChIP in droplet assay in comparison with conventional methods. The proposed technology dramatically reduces analytical time from a few days to 7 hours, simplifies the ChIP protocol and decreases the number of cells required by 100 fold while maintaining a high degree of sensitivity and specificity. Therefore this droplet-based ChIP assay represents a new, highly advantageous and convenient approach to epigenetic analyses.

Ourliac-Garnier I, Londoño-Vallejo A (2017 Jan 1)
Telomere Length Analysis by Quantitative Fluorescent in Situ Hybridization (Q-FISH)

Methods in Molecular Biology : 29-39 : DOI : 10.1007/978-1-4939-6892-3_3

Résumé

Length is a functional parameter of telomeres, the nucleoprotein structures that protect chromosome ends. The availability of highly specific, high affinity probes for telomeric repeat sequences allowed the development of quantitative approaches aimed at measuring telomere length directly on chromosomes or in interphase nuclei. Here, we describe a
general method for telomere quantitative FISH on metaphase chromosomes and discuss its most common applications in research