REGULATION OF TELOMERE LENGTH BY EPIGENETIC CHANGES IN THE SUBTELOMERIC REGION

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INTRODUCTION

Telomeres are non-coding DNA sequences that protect the ends of chromosomes from DNA repair and degradation. In vertebrates, telomeres consist of TTAGGG repeats.
The subtelomeric regions located next to telomeres are also enriched in repetitive DNA.

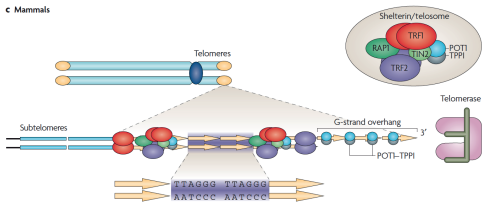

Figure 1: Structure of telomeres and subtelomeres in mammals (María A. Blasco, (2007))

Telomeres are thought to be maintained by at least two mechanisms:

- **Telomerase activity:** It is essential to germinal cells and cells that are in continuous division. But in most somatic cells, telomerase is expressed at very low levels.
- **Alternative lengthening of telomeres (ALT):** This mechanism relies on homologous recombination between telomeric sequences.

Most cancer cells are telomerase-positive and can generate *de novo* telomeric sequences allowing constant proliferation. Some cancer cells are not capable to activate telomerase and they use the ALT system.

Telomeric and subtelomeric chromatin contains histone modifications that are heterochromatin hallmarks such as H4K20 and H3K9 trimethylation, and HP1 heterochromatin isoforms. Furthermore, Subtelomeric DNA can be also methylated by DNA methyltransferases

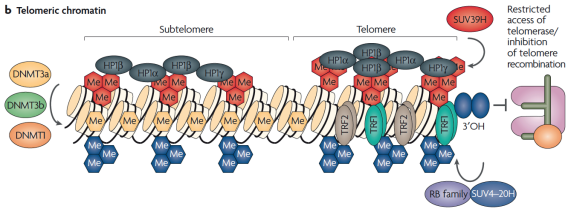

Figure 2: Epigenetic modifications at mammalian subtelomeric and telomeric regions (María A. Blasco, (2007))

Objective

The main goal of this review is to study the possible relationship between changes in the subtelomeric region and changes in the length of telomeres.

METHODS

Search of information

This review has been realized searching for different articles related to the subject and published during the last 10 years. Different Databases were used such as NCBI and WoK.

EPIGENETIC CHANGES RELATED TO TELOMERE LENGHTENING

- In **cells without histone methyltransferases**, HRK9 dimethylation and trimethylation are reduced and the telomere is longer.
- In **cells without DNA methyltransferases** a general hipomethylation is observed. In consequence, there is an increase of recombination and telomere length. After restoring DNA methyltransferases we can observe a decrease in both. This mechanism could take place due to the better telomerase acces to telomeres.
- In **telomerase-negative cells**, telomeres are shorter. These cells show decreased trimethylation of H3K9 and H3K20 in telomeric and subtelomeric region, as well as decreased subtelomeric DNA methylation. It is thought that this is due to the possible activation of ALT system.

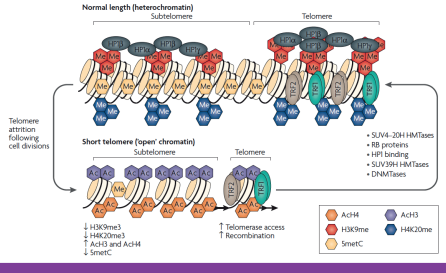

Figure 3: A model for the role of epigenetic modifications in telomere-length control (María A. Blasco (2007))

SUBTELOMERIC METHYLATION AND TERRA

- **Telomeric Repeat Containing RNA (TERRA)** is comprised of subtelomere and telomere-derived sequences.
- TERRA levels oscillate from low to high during cell cycle and regulate telomere lengthening.
- **Transcription Start Sites (TSS)** of TERRA and their promoter are situated in the subtelomeric region. Some studies showed a relationship between epigenetic changes in this region and TERRA levels. However, the specific connection between TERRA and telomere lengthening is still unknown.

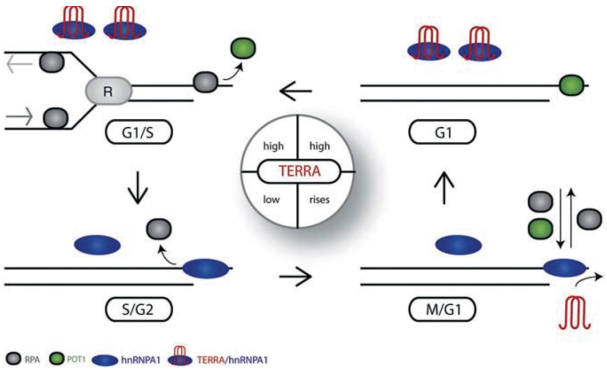

Figure 4: Cell cycle-dependent changes in total TERRA levels/TERRA-telomere colocalizations might control telomere end protection (Maicher A. et al. (2014))

SUBTELOMERIC METHYLATION AND TELOMERE LENGTHENING IN CANCER CELLS

Few studies have been carried out related to that and **controversy** is the word to summarize them. Some of them showed a small negative correlations between subtelomeric methylation and telomere lengthening, but others showed no significant relation. Furthermore, all the studies were made in different conditions; therefore, it is difficult to compare their results.

CONCLUSIONS

- In both **telomerase - positive and negative cells,** it has been observed that there are some especific correlations between epigenetic changes and telomere length. However, the mechanism is not known yet. It is said that TERRA has a key role in this relationship. Therefore, in a future TERRA might be a therapeutic target for some cancer therapies.
- In **cancer cells** the relationship is even more enigmatic due to the fact that, in most cases, their DNA has a general hipomethylation and it is possible that the effects of epigenetic changes in the subtelomeric region are hidden.
- Nowadays, we are far from knowing the certain relationship between epigenetic changes in the subtelomeric region and the telomere length. Therefore, it is necessary to carry out more studies to get to the heart of the matter.

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