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Review

Telomeric position effect: From the yeast paradigm to human pathologies?

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Abstract

Alteration of the epigenome is associated with a wide range of human diseases. Therefore, deciphering the pathways that regulate the epigenetic modulation of gene expression is a major milestone for the understanding of diverse biological mechanisms and subsequently human pathologies. Although often evoked, little is known on the implication of telomeric position effect, a silencing mechanism combining telomere architecture and classical heterochromatin features, in human cells. Nevertheless, this particular silencing mechanism has been investigated in different organisms and several ingredients are likely conserved during evolution. Subtelomeres are highly dynamic regions near the end of the chromosomes that are prone to recombination and may buffer or facilitate the spreading of silencing that emanates from the telomere. Therefore, the composition and integrity of these regions also concur to the propensity of telomeres to regulate the expression, replication and recombination of adjacent regions. Here we describe the similarities and disparities that exist among the different species at chromosome ends with regard to telomeric silencing regulation with a special accent on its implication in numerous human pathologies.
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1. Introduction

The organization of genomic DNA has greatly evolved from unicellular to complex organisms. Despite the increasing complexity of the information carried by the DNA sequence throughout evolution and subsequently, the chromatin architecture that controls the folding of the genome within the nucleus, shared mechanisms orchestrate the epigenetic regulation of chromosome organization and its influence on genome functions. Indeed, it is now evident that chromatin structure plays an important role in regulating gene transcription by providing the proper subnuclear environment to ensure spatial and temporal gene expression. Eukaryotic chromatin is organized into two distinct and interconvertible states, euchromatin and heterochromatin. Each chromatin state can be defined by its level of compaction, the positioning and the spacing of the nucleosomes, its histone code, the covalent modification of the underlying DNA, its non-histone binding factors, the spatial localization within the nucleoplasm and its dynamics during cell cycle.

Heterochromatin was originally described as a portion of the genome deeply stained from metaphase to interphase associated with the pericentric regions, telomeres and some interstitial domains. In higher eukaryotes, constitutive heterochromatin is enriched in methylated DNA, histone H3K9 di- and trimethylation, HP1 binding and can spread over genomic regions inducing thereby the silencing of other sequences. A classical example of silencing is known as position effect variegation (PEV) and occurs when a gene is juxtaposed to heterochromatin. The nature of telomeric and subtelomeric chromatin differs from global constitutive heterochromatin due to the specificity of its DNA sequences, the particular structure of its nucleosomal

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fiber and the binding of specific factors. However, despite these structural differences, most telomeres and subtelomeres from *Saccharomyces cerevisiae* to *Homo sapiens* repress natural or artificially inserted neighboring genes by a mechanism named *T*elomeric *P*osition *E*ffect (TPE) (Fig. 1). Such a widespread conservation of telomeric silencing among eukaryotes suggests that is fundamental for telomere function and consequently chromosome integrity.

The mechanisms of TPE are well documented in *S. cerevisiae* and this review will focus on the cross talks between telomere structure and silencing in different species, with a special emphasis on the emerging role of TPE in human cells and a large spectrum of pathologies.

2. TPE discovery and definition

TPE has been extensively studied in baker's yeast, although it was revealed in this model organism five years after its discovery in *Drosophila melanogaster* [1–3]. Unlike Drosophila, telomeres in *Saccharomyces cerevisiae* are constituted of stretches of highly repetitive telomerase-added repeats and thus resemble most of the eukaryotic telomeres therefore constituting a powerful genetic system for the study of TPE.

TPE in yeast was first demonstrated by insertion of a construct containing a *URA3* marker next to an array of telomeric repeats. Integration of this construct at the subtelomeric *ADH4* locus, close to the VII-L telomere, deletes the terminal 15 kb of the chromosome and positions the *URA3* promoter 1.1 kb from the newly formed telomere, termed truncated VII-L. Expression of the *URA3* gene allows growth of the cells on plates lacking uracil. However, on plates containing a drug toxic for cells expressing *URA3* (5-fluoro-orotic acid or 5-FOA), 20–60% of the cells were still able to grow, suggesting that the *URA3* was silenced in the vicinity of the telomere [4]. Some of the features of TPE were concomitantly described, such as the stochastic reversibility, since the same cells plated onto a medium without uracil can still grow without the amino acid; or the promoter independence and expression variegation, since expression of the *ADE2* gene is also repressed in the same context and colonies obtained present white (ade2+) and red (ade2−) sectors.

TPE has been thoroughly investigated in yeast and its classical definition was first established in this model as a silencing effect originating from the telomere and consisting in an inward Sir-dependent heterochromatin spreading. Since then numerous results (that we will discuss below) have been reported from different organisms on the requirements, the modulations, or the chromosomal and nuclear contexts of this silencing effect. This will lead us to broaden the definition of TPE and to consider it at the level of functional genomic and nuclear organization.

3. What is required for TPE?

Experiments on TPE in *S. cerevisiae* were mostly performed at the truncated VII-L chromosome [4] but also at several other truncated [5] and natural telomeres [6], allowing the identification of more than 50 proteins that can modulate TPE. However, among deletion mutants of these different proteins, only a few exhibit a specific and complete suppression

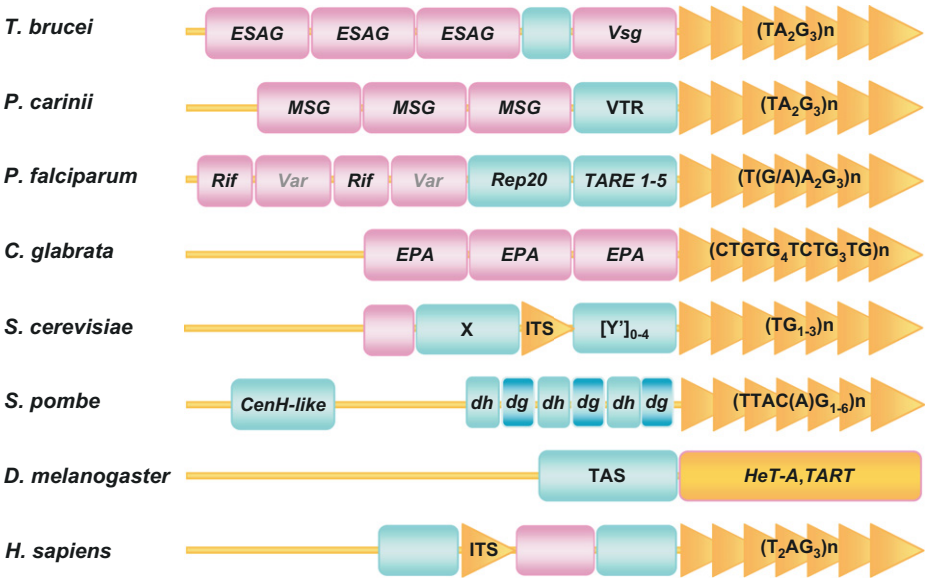

Fig. 1. Comparison of chromosome ends in various eukaryotic organisms known to exhibit telomeric position effect. In eukaryotes, the subtelomeres are patchworks of genes (pink rectangles) interspersed within repeated elements (blue rectangles). At least in baker's yeast and human, large polymorphic blocks of repeated sequences are distributed between the different chromosomes and subtelomeres contain genes. The simple repeats that constitute the telomeric DNA of many organisms and that are synthesized by the telomerase enzyme are represented by triangles and the specific sequence is indicated for every organism. The end of chromosomes of *D. melanogaster* is not synthesized by a telomerase enzyme but is formed through the retrotransposition of the non-LTR retroptransposons *HeT-A* and *TART* (yellow rectangle). VTR, *V*ariable *T*andem *R*epeat; TAS, *T*elomere *A*ssociated *R*epeat; ITS, *I*nterstitial *T*elomeric *R*epeats; ESAG, *Trypanosoma brucei E*xpression *S*ite *A*ssociated *G*ene; Vsg, variant coat protein; MSG, *Pseudomonas carinii* surface glycoprotein gene. Var, Rif, *Plasmodium falciparum* subtelomeric genes; *Rep20*, *TARE 1–5*, subtelomeric repeats. EPA, *Candida glabrata* adhesin gene. Dh, dg, *Schizosaccharomyces pombe* subtelomeric repeats.

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