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Review

# Telomere length regulation in budding yeasts

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ABSTRACT

**Telomeres are the nucleoprotein caps of chromosomes. Their length must be tightly regulated in order to maintain the stability of the genome. This is achieved by the intricate network of interactions between different proteins and protein–RNA complexes. Different organisms use various mechanisms for telomere length homeostasis. However, details of these mechanisms are not yet completely understood. In this review we have summarized our latest achievements in the understanding of telomere length regulation in budding yeasts.**


## 1. Introduction

The ends of eukaryotic chromosomes, called telomeres, shield chromosomal DNA from the action of cellular nucleases. The next problem the telomeres solve is to prevent recognition as DSBs by the repair machinery, since this would lead to chromosomal fusions and eventually to loss of the genetic material. Both of these functions are achieved by the special organization of telomeres. Telomeric DNA, which consists of short GC-rich repeats, has a double-stranded region and a single-stranded G-rich 3′-overhang. These two regions are bound by specific sets of proteins, which distinguish telomeric chromatin from internal parts of the chromosome. Exact sequences of telomeric DNA and protein composition of telomeres vary between different organisms [1].

Telomeres shorten with each cell division due to what is known as the end-replication problem. RNA–protein complex telomerase reverse transcribes telomeric DNA, using its own RNA template, to counteract this problem [2]. Telomerase is crucial for the viability of unicellular eukaryotic organisms, such as ciliates and yeasts [3].

Genes adjacent to telomeres are subjected to silencing known as "telomere position effect" (TPE) [4]. Nevertheless, the subtelomeric regions contain promoters directed towards the ends of the chromosomes. The product of transcription from these promoters is a special class of non-coding RNAs called telomeric repeat-containing RNA, or TERRA [5]. TERRA is an important component of telomeric chromatin, as it participates in many aspects of telomere biogenesis [6]. However, its role is still poorly understood.

Budding yeasts are members of the subphylum *Saccharomycotina* of the phylum *Ascomycota* of the *Fungi* kingdom. Budding yeasts have proven to be useful models for studying diverse cellular processes. Research of telomere biology has been conducted on several representatives of the *Saccharomycotina* group. The relative evolutionary relationship between budding yeasts, that are described in this paper, is schematically depicted in Fig. 1.

Herein, we review mechanisms of telomere length regulation by telomerase and telomeric proteins in budding yeasts. The best studied organism in this field is *Saccharomyces cerevisiae*, so it will be the focus of our review. Comparisons with other model budding yeasts, such as *Candida albicans* or *Kluyveromyces lactis*, will be presented when possible.

## 2. Budding yeasts telomere structure

Telomeric repeats in budding yeasts have undergone dramatic changes during evolution: their sequences differ greatly from the canonical TTAGGG repeat (found in many organisms including mammals); their lengths lie within the 8–25 bp range, and telomeric repeats are often degenerate [7]. For example, *S. cerevisiae* repeats are heterogeneous $T(G)_{2\text{-}3}(TG)_{1\text{-}6}$, whereas *C. albicans* are homogenous ACGGATGTCTAACTTCTTGGTGT.

In *S. cerevisiae*, the double-stranded region of telomeres is bound by the Rap1 protein through its MYB domain [8]. Rap1

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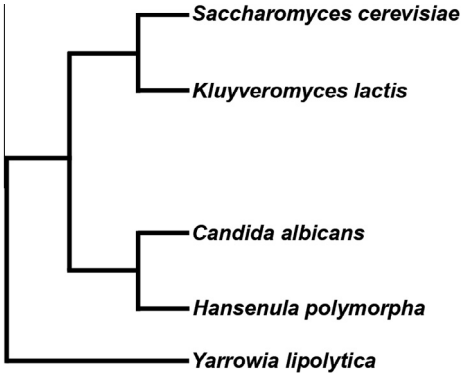


**Fig. 1.** The schematic representation of the phylogenetic relationship between budding yeasts described in the present work (adapted from [93]).

recruits two sets of additional proteins, interacting with its C-terminal domain. One of them (Sir3 and Sir4) is responsible for the TPE [9]. Another one (Rif1 and Rif2) is primarily required for telomere length regulation (Fig. 2A) [10,11]. Rap1 also prevents inappropriate exonuclease-mediated resection at telomeres and telomere fusions by inhibiting the non-homologous end-joining (NHEJ) repair pathway [12,13]. The single-stranded 3′-overhang is bound by Cdc13. Cdc13 together with its two interacting partners Stn1 and Ten1 forms trimeric RPA-like complex (CST complex) (Fig. 2A) [14]. The CST complex prevents recognition of telomeres by repair machinery and protects the C-strand from degradation by nucleases [15]. CST effectively competes with RPA for single-stranded telomere binding and inhibits RPA (and checkpoint kinase Mec1) accumulation. However, it does not affect binding of the MRX complex (and another checkpoint kinase Tel1) to DNA ends [16]. Apart from its capping function, Cdc13 regulates both G-strand and C-strand telomere synthesis, as it participates in both telomerase and replicative polymerase recruitment [17,18]. The Ku70/Ku80 heterodimer is another important telomere protein. Its exact location is still unknown, but it is thought to be the junction between double and single stranded regions of telomeric DNA (Fig. 2A) [19]. Ku70/Ku80 complex also plays role in preventing excessive C-strand resection [20,21]. *S. cerevisiae* has another MYB domain containing protein Tbf1 that binds TTAGGG sequences, located in subtelomeric regions (Fig. 2A) [22]. Tbf1 plays role in the regulation of the length of telomeres [23,24]. The MYB domain of Tbf1 is related to the MYB domains of mammalian telomere binding factors TRF1 and TRF2 [25].

Recent biochemical and structural characterization of Rap1, Rif1 and Rif2 binding to telomeric DNA suggests a model of a higher-order organization of telomeres. Through Rif1 tetramerization, polymerization of Rif2 and interaction of both with Rap1 all three proteins appear to be involved in the formation of a "Velcro"-like structure. Such organization provides necessary protection for telomeric DNA, but at the same time is dynamic, since it is composed of multiple weak interactions and can be easily disassembled [26].

Mammalian telomeres were shown to form a fold-back structure (t-loop) by interaction of the 3′-overhang with double-stranded telomeric DNA [27,28]. T-loop formation has been implicated in telomere capping. Although technical insufficiencies hamper visualization of t-loops in budding yeasts, and yeast telo-

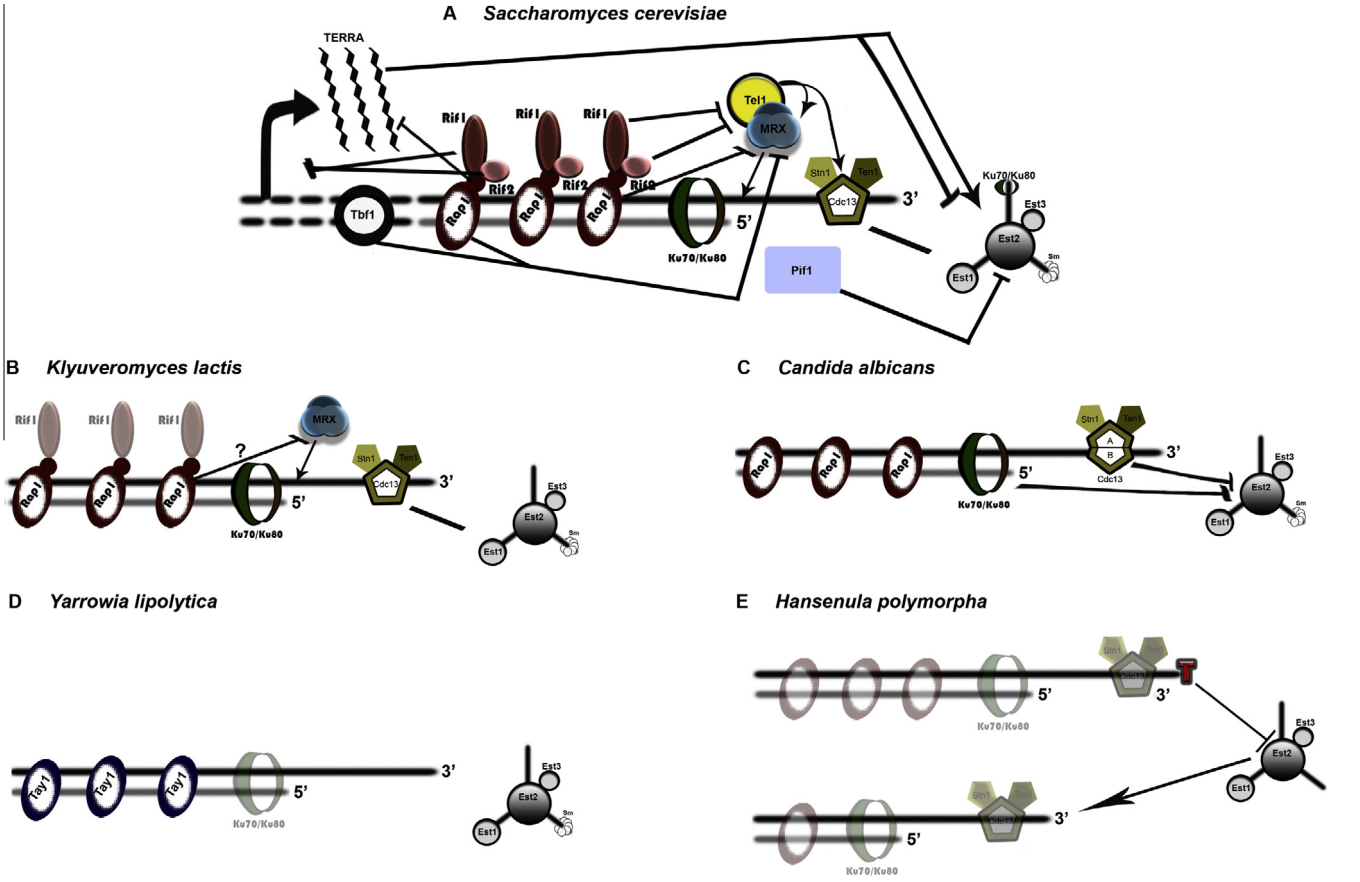


**Fig. 2.** Telomere structure and pathways regulating telomere-telomerase interaction in budding yeasts: (A) *S. cerevisiae*, (B) *K. lactis*, (C) *C. albicans*, (D) *Y. lipolytica*, (E) *H. polymorpha*. Black and grey parallel lines represent telomeric DNA, black dashed line represent subtelomeric DNA. Arrows represent activating effect, blunt arrows represent inhibitory effect. The line, connecting Cdc13 and Est1, represents their interaction. Lines, which connect Est2 and other components of telomerase, represent telomerase RNA. Proteins, the presence of which at telomeres is expected, but not confirmed, are lightened (in B, D and E).

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