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Signalling networks in focus

The telomeric transcriptome: From fission yeast to mammals

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ABSTRACT

The ends of linear eukaryotic chromosomes are transcribed into different species of non-coding transcripts (the telomeric transcriptome), including TERRA (telomeric repeat-containing RNA) molecules; however, the functions associated with the telomeric transcriptome remain elusive. Experimental evidence accumulated during the past few years indicates that the transcriptional activity of telomeres is changed in cells in which the integrity of the telomeres or the heterochromatic state of chromosome ends is altered. On the contrary transcription of a telomere appears not to be influenced by its length. In this paper we briefly review the current state of knowledge on the composition, biogenesis, and regulation of the telomeric transcriptome from yeasts to humans. We also suggest a model in which TERRA is part of the DNA damage response triggered by dysfunctional telomeres and discuss the potential involvement of telomere transcription in the development of human pathologies.

Signalling network facts

- Telomeres – the physical ends of linear eukaryotic chromosomes – are transcribed by RNA polymerase II into a complex array of long non-coding RNA molecules including telomeric repeat-containing RNA (TERRA).
- TERRA molecules associate with telomeres possibly through interactions with telomeric factors.
- The epigenetic state and the integrity of telomeres, but not telomere length, influence the steady-state levels of TERRA.
- TERRA might participate in the DNA damage response triggered by dysfunctional telomeres.

1. Introduction

The ends of linear eukaryotic chromosomes are capped by specialized nucleoprotein structures called telomeres. Telomeres are composed of polarized double-stranded repetitive DNA sequences that contain a strand rich in guanines (the G-rich strand) oriented 5′–3′ toward the end of the chromosome and a complementary strand rich in cytosines (the C-rich strand). The G-rich strand protrudes over its complement to form a single-stranded overhang (Fig. 1). In vertebrates, telomeric repeats are 5′-TTAGGG-3′ units that extend for 2–50 kb, whereas in the fission yeast *Schizosaccharomyces pombe* they comprise the degenerated 5′-TTAC(A)GG(G_{1-4})-3′ sequence and extend for about 300 bp. The G overhang ranges from 50 to 500 bases in vertebrates and from 12 to more than 30 bases in yeasts (Jain and Cooper, 2010; O'Sullivan and Karlseder, 2010). Immediately adjacent to the telomeric tract, a subtelomeric region spreads out toward the centromere. Mammalian subtelomeres contain non-telomeric sequences interspersed with degenerated and perfect 5′-TTAGGG-3′ repeats. In fission yeast, chromosomes I and II comprise the subtelomeric elements STE1, STE2, and STE3, whereas ribosomal DNA repeats are juxtaposed with telomeres on chromosome III (Jain and Cooper, 2010; O'Sullivan and Karlseder, 2010).

A conserved protein complex called shelterin binds directly to telomeres and plays important roles in regulating telomere length homeostasis and telomere integrity by modulating enzymatic activities and DNA conformations (Jain and Cooper, 2010; O'Sullivan and Karlseder, 2010). Human shelterin comprises TRF1 and TRF2, which bind directly to the double-stranded (TTAGGG)n tract and recruit the other shelterin components Rap1, TIN2, TPP1, and POT1. POT1 proteins also bind directly to the single-stranded G overhang (Fig. 1A; Jain and Cooper, 2010; O'Sullivan and Karlseder, 2010). In fission yeast, the telomeric proteins Rap1, Poz1, Tpz1, Pot1, and Ccq1 congregate around the double-stranded DNA binding protein Taz1, the ortholog of TRF1 and TRF2, to form a complex that functionally and structurally resembles mammalian shelterin (Fig. 1B; Jain and Cooper, 2010; O'Sullivan and Karlseder, 2010). Besides the shelterin complex, chromosome ends are also enriched with heterochromatin marks such as histone H3 trimethylated at lysine 9 (H3K9me3), histone H4 trimethylated at lysine 20 (H4K20me3), DNA methylated at 5-methylcytosine, and specific heterochromatin proteins such as HP1 isoforms in mammals and

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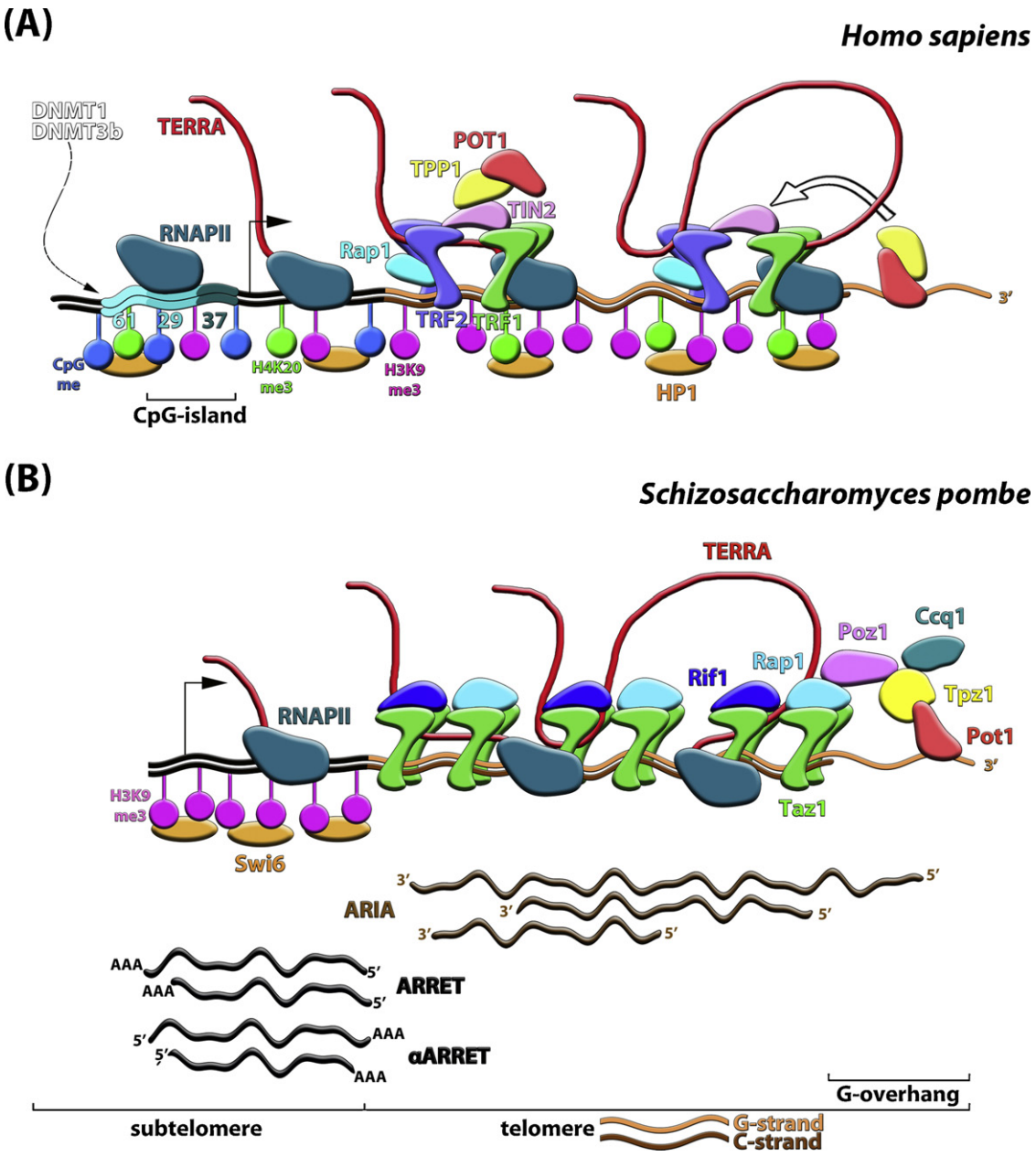

Figure 1. *The molecular composition of mammalian and fission yeast chromosome ends.* (A) Human telomeric repeats are bound by the shelterin complex, which is composed of the six proteins TRF1, TRF2, Rap1, TIN2, TPP1, and POT1. Telomeric repeat-containing RNA (TERRA) is transcribed from a defined start site (black arrow) toward the end of the chromosome and possibly associates with TRF1 and TRF2. RNAPII drives the transcription of TERRA from subtelomeric CpG dinucleotide-rich promoters. Telomeres and subtelomeres are enriched in heterochromatin marks, including HP1, H3K9me3, H4K20me3, and methylated CpG dinucleotides. (B) *Schizosaccharomyces pombe* telomeric repeats are bound by a shelterin-like complex consisting of Taz1, Rap1, Poz1, Tpz1, Pot1, and Ccq1. TERRA is transcribed from a defined start site (black arrow) toward the end of the chromosome and remains associated with telomeres, possibly through interaction with Taz1, as Taz1 is the functional ortholog of mammalian TRF1 and TRF2 proteins. Besides TERRA, *S. pombe* chromosome ends are transcribed into ARIA, ARRET, and αARRET molecules. Whether these RNA species associate with telomeric chromatin is not known. *S. pombe* chromosome ends are enriched in heterochromatin marks, including Swi6 and H3K9me3. The mammalian and *S. pombe* chromosome ends shown are not to scale.

Swi6 in fission yeast (Fig. 1; Benetti et al., 2007; Blasco, 2007; Kanoh et al., 2005). Consistent with their heterochromatic state, telomeres are able to repress the transcription of nearby genes through a phenomenon known as the telomere position effect (Ottaviani et al., 2008). As for shelterin, the establishment of heterochromatin at telomeres contributes to the strict regulation of telomere length homeostasis and telomere stability (Benetti et al., 2007; Blasco, 2007). Alterations to the epigenetic state of mammalian telomeres and subtelomeres are associated with several human pathologies, including cancer and mental retardation, indicating that these regions are of great clinical importance (Blasco, 2007).

When they were discovered, telomeres were thought to be transcriptionally silent. This belief was invalidated by the finding that telomeres are transcribed into telomeric repeat-containing RNA (TERRA) molecules in several eukaryotes, including mammals, birds, zebra fish, budding yeast, Arabidopsis, and fission yeast (Azzalin et al., 2007; Bah et al., 2011; Greenwood and Cooper, 2011; Luke et al., 2008; Schoeftner and Blasco, 2008; Solovei et al., 1994; Vrbsky et al., 2010). The discovery of TERRA has redefined the telomere as a complex nucleoprotein structure consisting not only of DNA and proteins but also of RNA. In this paper we briefly review the current state of knowledge on telomeric transcription, focusing on information gleaned from mammalian cultured cells