**News & Views**

**TERRA Incognita at chromosome ends**

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Telomeres are transcribed in long noncoding RNA named TERRA. Although TERRA functions have been extensively investigated, the role of TERRA in telomerase recruitment and regulation is still elusive.

In this issue of *EMBO Reports*, Moravec et al report in *Schizosaccharomyces pombe* that telomere shortening induces the expression of TERRA [1]. They show that polyadenylated TERRA molecules specifically associate with the telomerase catalytic subunit and stimulate telomerase-mediated elongation of the telomere from which the TERRA molecules originate. Strikingly, their results indicate that shaping the 3' end of telomere transcripts controls telomerase activity.

**See also:** M Moravec *et al* (July 2016)

Telomeres consist of DNA repeats associated with proteins, which constitutes a peculiar form of chromatin that protects the ends of chromosomes from degradation, fusion, and activation of DNA damage responses. Telomeres comprise arrays of G-rich tandem DNA repeats with a single-stranded extension on the 3' strand called G-tail. Telomeric DNA is bound by the shelterin complex that bridges the duplex telomeric DNA to the G-tail. Various combinations of this canonical structure are found in different organisms. In contrast to yeast telomeres that adopt a non-nucleosomal chromatin structure, mammalian telomeric chromatin contains arrays of shelterin complexes flanked by nucleosomes. Despite these differences, telomeres and subtelomeric regions are heterochromatic in nature and create a transcriptionally repressive chromatin environment. In spite of this, telomeres were found to be transcribed by RNA polymerase II, which reads the G-rich telomeric strand to generate G-rich telomeric repeat-containing RNA, called TERRA [2]. Transcription of TERRA starts within the adjacent subtelomeric sequences and includes a variable number of telomeric G-rich sequences. TERRA was initially discovered in mammalian cells and then in other eukaryotes including budding yeast, zebrafish, and plants [3]. TERRA transcripts have been proposed to have several functions including telomeric heterochromatin formation, capping of chromosome ends, telomere replication, and regulation of telomerase activity; however, their precise molecular roles remain to be carefully elucidated. Moreover, conflicting data have been reported regarding the localization of TERRA and its role in telomerase recruitment and activity. For instance, in budding yeast accumulation of TERRA induced by the inactivation of the Rat1 5' to 3' exonuclease affected telomerase-mediated telomere elongation [4], while in another study TERRA molecules were proposed to participate in telomerase-dependent elongation of the transcribed telomere by aggregating telomerase molecules at short telomeres [5,6]. Similarly, human TERRA was shown *in vitro* to be a natural ligand and direct inhibitor of human telomerase [7,8]; however, overexpression of TERRA in cells lacking the two DNA methyltransferases DNMT1 and DNMT3b did not affect telomerase activity [9]. These examples point out the need for unifying models integrating all these observations.

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\[\ldots\text{shaping the 3'}\text{ ends of TERRA transcripts by transcription termination may control telomerase activity}\]\n
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would increase TERRA transcription and release of polyadenylated TERRA into the nucleoplasm, where it would interact with telomerase and bring it back to its telomere of origin. In agreement with the model suggested by Cusanelli et al. in budding yeast, interaction of telomerase with polyadenylated TERRA would promote telomerase recruitment and elongation of the telomere from which the TERRA molecules originate. Two main questions remain to be answered. First, is the interaction between polyadenylated TERRA and the catalytic subunit of telomerase direct? This question could be solved by the use of the CRAC method (cross-linking and analysis of cDNA) developed by Markus Bohnsack to identify potential interaction sites of telomerase with polyadenylated TERRA. The second question is how is polyadenylated TERRA with short telomeric tracts generated? Overall, the work by Moravec has three important merits: (i) It shows that polyadenylated TERRA interacts with telomerase, (ii) it provides evidence that telomere transcription stimulates telomerase-mediated telomere elongation in cis in an organism with human-like telomeres, and (iii) it proposes that different TERRA molecules may have opposing effects on telomerase activity. In Fig 1, we speculate how transcription termination could shape the 3′ ends of TERRA transcripts and lead to different TERRA molecules with opposing effects. TERRA molecules processed by the cleavage and polyadenylation factor (CPF)–cleavage factor (CF) complex would generate polyadenylated TERRA with no (or very short) telomeric sequences. These polyadenylated TERRA molecules would promote telomerase activity by nucleating telomerase at chromosome ends. Other pathways involved in TERRA termination—that remain to be determined—could generate TERRA with long telomeric tracts that would exert an inhibitory effect on telomerase. This hypothesis could reconcile some of the apparently conflicting results described above. After many efforts to understand how TERRA transcription is initiated, this work from Azzalin and co-workers points out the need to determine the mechanisms underlying TERRA transcription termination. Indeed, shaping the 3′ ends of TERRA transcripts by transcription termination may control telomerase activity.

References