A study published in this issue of EMBO Journal dissects the properties of elongated telomeres generated by telomerase as opposed to alternative (ALT) recombination mechanisms. In a result that breaks with the current paradigm, Pickett et al find that many characteristics previously ascribed to the ALT pathway are the property of the elongated telomere itself.

Telomeres are the nucleoprotein structures at the termini of eukaryotic chromosomes that are necessary for chromosomal capping and genomic stability. Telomeric DNA is made up of G+T rich simple sequence DNA that is normally added by the ribonucleoprotein reverse transcriptase telomerase. In human somatic cells, the low levels of telomerase cannot maintain the length of the telomere tracts and hence precipitates senescence checkpoint(s). If bypassed either by a mutation in a checkpoint component or by viral transformation, telomere tracts continue to erode. This erosion leads to the inevitable initiation of a genomic crisis. Immortalized survivors arising from this process have an efficient telomere addition system. Most often this involves the activation of telomerase, giving rise to short but stable telomeres. This is consistent with the activation of telomerase in the majority of oncogenic tumours. However, less frequently, telomeres are elongated through alternative (ALT) recombinational mechanism(s) (Bryan et al, 1997).

ALT cells have a number of unique properties. First, they contain extremely elongated telomeres. These >20 kb telomeres may be generated by rolling circle and/or inter-chromosomal exchange (Henson et al, 2002). Second, ALT telomeres are highly unstable producing cells containing multiple truncated telomeres (Murnane et al, 1994). Third, ALT cells contain a unique subset of promyeloctic leukaemia bodies, termed ALT-associated PML bodies (APBs) (Yeager et al, 1999). The APB contains a high concentration of Rad51 and other recombinational and repair enzymes, the telomere-binding protein TRF2 and telomeric DNA. ALT cells also display a high level of telomere dysfunction-initiated foci (TIF). A central issue in understanding the characteristics of telomeres in ALT tumours is to distinguish the properties that arise from the ALT mechanism versus elongated telomeres per se. Reddel and colleagues (Pickett et al, 2009) have approached this problem by assaying the characteristics of telomeres elongated by the over-expression of telomerase, allowing immortalized tissue culture cells to form telomeres that reach sizes two-fold greater than found in the progenitor cell line. The authors find that these elongated telomeres recapitulate some of the properties of ALT telomeres. First, telomeres in both cases are unstable, albeit more extreme in ALT cells, and can undergo deletion of telomere tract accompanied by the accumulation of t-circles. This process is the most likely outcome of recombinational deletion of the terminal t-loops, structures in which the 3' terminus invades telomere distal telomere sequence (Griffith et al, 1999) forming a Holliday junction (Figure 1). Hence, the recombinational resolution of t-loops is most likely to be the mechanism of recombinational trimming of telomeres (Figure 1). These data suggest that t-loop formation may not only be a means of telomerase regulation but may possibly function as a recombinational sensor of overall telomere size.

The second highly unusual observation was found in two sets of cell lines where a small, but significant, subset of telomerase-expressing cells form APB-like structures. These data suggest that telomere size has an unexpected function in APB formation, although the increased length is not sufficient for a high efficiency of APB generation.

Significantly, the interchange of telomeric recombination that may serve as a mechanism for ALT elongation is not present in telomerase-elongated telomeres. Similarly, the high levels of telomeric sister chromatid exchange (T-SCE) (Londono-Vallejo et al, 2004) are unique to ALT cells. T-SCE may be either involved in the mechanism of telomere elongation in ALT cells or secondary to the high levels of recombinational enzymes in APB structures. Similarly, as opposed to ALT cells, there is no increase in the abundance of TIF (de Lange, 2002).

What is the advantage of telomere trimming? One possibility relates to the strong selective advantage to maintain telomere size homeostasis. For example, telomeres of differing size may cause aberrant telomere–telomere or telomere–nuclear membrane associations. Such a possibility has been previously proposed to explain the drive towards homogeneity in the size of yeast telomeres through a similar rapid deletion process (Li and Lustig, 1996; Lustig, 2003). Trimming may then be particularly important if...
elongated telomeres cause a breakdown in the normally efficient feedback control mechanism (Marcand et al., 1997; Smogorzewska et al., 2000). Although not a mutually exclusive possibility, elongated telomeres may result in alterations in the structure of the protective shelterin complex (de Lange, 2005) leading to telomere dysfunction. Trimming may select for sizes that stabilize telomere chromatin and hence restore telomere function.

The elucidation of properties elicited by elongated telomeres per se will allow further investigation of the size-independent mechanisms contributing to the generation of ALT telomeres.

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