EDITORIAL

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Unraveling the ends

Deciphering the complexity of events at telomeres has enhanced understanding of how telomeres function to maintain genome integrity and how their dysfunction gives rise to human disease.

Telomeres distinguish the linear ends of chromosomes from DNA breaks and are essential for genome integrity. Their unique nucleoprotein structure is composed of tandem repeats of DNA sequences, which are synthesized by the telomerase enzyme, and specialized telomeric proteins that protect the DNA ends and prevent their recognition as sites of DNA damage. Because replicative DNA polymerases cannot duplicate the extreme 3′ ends of chromosomes, and telomerase is repressed in normal somatic cells, telomeres progressively shorten with each cell-division cycle and ultimately trigger replicative senescence when they reach a critically short length. The central role of telomere length in determining cellular lifespan places telomeres at the nexus of cellular and molecular biology as well as cancer and aging research. In this issue, we present a special Focus on Telomeres (http://www.nature.com/nsmb/focus/telomeres2015/index.html) that explores the mechanisms of telomere protection and length regulation in mammalian cells; the manner in which regulation is circumvented in cancer cells to expand their proliferative capacity; and the clinical implications of the loss of these essential telomeric functions.

The telomerase enzyme is a ribonucleoprotein complex whose catalytic core consists of a reverse transcriptase (TERT) directed by an RNA (TR) that binds complementary telomeric repeat sequences and provides the template for processive DNA synthesis. The mechanism of telomerase activity is examined in a Commentary by Lee and Yang (p 844). The authors propose a new DNA-hairpin model, based on structural comparisons between TERT and DNA polymerases that promote translesion synthesis, which accounts for the unique ability of TERT to catalyze multiple cycles of telomere-repeat addition to chromosome 3′ ends.

In mammalian cells, telomeric DNA is protected by the protein complex shelterin, which inhibits multiple pathways of DNA-damage sensing and repair and prevents chromosome end-to-end fusion or recombination events. Shelterin not only confers stability to linear chromosome ends but also collaborates with telomerase in regulating synthesis of telomeric DNA repeats and determining the threshold telomere lengths that support or restrict cell proliferation. In their Perspective, Hockemeyer and Collins (p 848) discuss recent insights into how telomerase activity is controlled at telomeres through telomerase-shelterin interactions and how these two complexes may coordinate telomere-length homeostasis by regulating telomerase recruitment or productive substrate engagement at the enzyme active site.

The protective function of the shelterin complex is explored by Arnoult and Karlseder (p 859), who review the DNA-damage signaling and repair pathways that are repressed at telomeres and discuss the roles of DNA-repair factors in establishing and maintaining a protected telomere structure during and after telomere replication. They also consider how proliferative barriers are controlled by telomere deprotection and describe the emerging role of telomeres as active regulators of programs that determine cellular fate.

Cancer cells can overcome the problem of telomere attrition by activating telomere length–maintenance programs that support continued replication potential. This can be accomplished through reactivation of telomerase expression or through a telomerase-independent mechanism, called alternative lengthening of telomeres (ALT), that involves homology-directed telomere synthesis. In their Review (p 875), Pickett and Reddel discuss recent advances toward elucidation of the ALT mechanism as well as how this alternative pathway is repressed in normal cells.

The clinical importance of understanding the mechanisms of telomere function is underscored by the observation that mutations that compromise telomere maintenance give rise to a family of inherited human telomere biology disorders that are defined by premature telomere shortening and are associated with increased cancer risk. Sarek, Marzec, Margalef and Boulton (p 867) review the modes of inheritance and cellular consequences of mutations associated with dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome; they also describe the molecular functions impaired by underlying mutations in shelterin or telomerase components and associated factors that promote telomerase biogenesis or that facilitate telomere replication and maintenance.

Finally, a Perspective from Rippe and Luke (p 853) discusses the roles of TERRAs, long noncoding RNAs (lncRNAs) composed of telomeric repeat sequences that hybridize with telomeric DNA and are components of telomeric heterochromatin. Transcribed from chromosome ends by RNA polymerase II, TERRA has been implicated in both telomerase-dependent and telomerase-independent telomere-length maintenance during replicative senescence and cancer, but its precise roles have remained elusive. The authors propose that TERRA function is determined by the state of its telomere targets and discuss models for these context-dependent activities.

The progress in unraveling the intricate mechanisms of telomere function highlights the challenge of maintaining linear chromosomes in a cellular environment that has evolved to eliminate DNA ends. It also provides fertile ground for future investigations that we look forward to seeing develop in the pages of *Nature Structural & Molecular Biology*. Last, we would like to thank our sponsors, Geron Corporation and Janssen Oncology, whose generous support has allowed Focus content to be made freely available for the next 6 months. As always, *Nature Structural & Molecular Biology* carries sole responsibility for all editorial content. ■