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Scientific Comment

Stressed ends: telomere attrition in chronic diseases[☆]

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Telomeres are DNA–protein structures that cap chromosomal ends and protect them from degradation. In vertebrates, these sequences are composed of long stretches of TTAGGG repeats that can extend for up to 15 kilobases (kb) in humans and 100 kb in rodents. The telomeric DNA is composed of a long double-stranded tract that ends in a short, single-stranded overhang. Telomeric DNA is bound by shelterin, a large multi-subunit protein complex that prevents the chromosome ends from being recognized as a DNA break, and inhibits inappropriate recombination. Inhibition or deletion of specific shelterin components results in a local DNA damage response at chromosome ends, leading to robust activation of DNA damage pathways and cell death. Due to the inability of DNA polymerases to fully replicate chromosome ends at the lagging strand, at every cell division there is a loss of up to 200 base pairs of telomeric DNA.¹ It is suggested that critically short telomeres carry insufficient shelterin components to avoid ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and ‘rad3-related’ (ATR) signaling cascades.² Accordingly, cells with short telomeres present classical DNA damage-responses, such as formation of telomere induced foci (TIFs), stabilization of p53, and activation of p21.² The telomerase ribonucleoprotein, which is able to synthesize telomeres from an RNA template, provides a compensatory mechanism to continuous telomere shortening.³ In humans however, telomerase is only active in stem and progenitor cells, and is not able to maintain telomere length throughout lifespan.⁴ In this regard, telomere shortening can be seen as a molecular clock for cellular aging.

The detrimental effects of telomere shortening can be seen in patients suffering from “telomeropathies”, a group of clinically diverse diseases where patients have mutations in different genes necessary for telomere maintenance.⁵ With the popularization of DNA sequencing technologies for clinical diagnostics, the number of diseases directly related to mutations in telomere biology genes has increased, along with the number of different genes mutated in these patients, and with the number of different mutations found in each gene. These diseases, which range from severe pediatric complications (such as bone marrow failure in dyskeratosis congenita and Hoyeraal–Hreidarsson syndromes) to adult-onset diseases (such as liver fibrosis and cirrhosis, as well as pulmonary fibrosis) share the same molecular determinant: telomeres that are at, or below, the first percentile in length when compared to age-matched controls. Interestingly, telomere length is a regulator of disease severity in patients harboring mutations in telomere biology genes, with more severe mutations causing more severe phenotypes at younger ages. In addition, in families with autosomal-dominant mutations, disease phenotypes are observed progressively earlier in age from one generation to the next, a process described as telomeric genetic anticipation.

Interestingly, in recent years, telomere attrition has also been described in a number of different conditions, ranging from depression to poor immune function and diabetes, where patients do not have mutations in telomerase biology genes.⁶ Most notably, shorter leukocyte telomere length (LTL) has been directly associated with cardiovascular disease⁷ and it has

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[☆] See paper by Colella et al. in Rev Bras Hematol Hemoter. 2017;XX(X):XX-XX.

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been proposed that LTL can be a relevant biomarker of cardiovascular aging.⁸ The prevalent theory is that inflammation and oxidative stress trigger a faster immune cell turnover, which in turn leads to a shorter LTL.⁹ This is in line with the data shown by Colella *et al.*, in this issue of the Brazilian Journal of Hematology and Hemotherapy.¹⁰ In their work, the authors analyzed telomere lengths from peripheral blood leukocytes of sickle cell disease (SCD) patients. The authors demonstrated by different methods that telomeres are significantly shorter in SCD patients in comparison to age-matched controls. In addition, within the cohort of SCD patients, telomere shortening correlated with disease severity, with homozygous mutant patients having significantly shorter telomeres than heterozygous patients. Moreover, patients on hydroxyurea also had significantly shorter telomeres when compared to patients not treated with the drug. Interestingly, in SCD patients, telomere length did not correlate with age, which indicates that in these patients the telomere attrition caused by the disease phenotype is significant enough to ablate the mild, gradual shortening of telomeres that occurs with natural tissue aging.

Combined, the results presented by Colella *et al.*, indicate that in SCD, inflammation and oxidative stress (elevated oxidative stress burden is a well-established occurrence in SCD) also contribute to telomere attrition.¹⁰ While future studies should continue to decipher the role of telomere length and human disease, and establish if telomere attrition plays a direct role in disease progression, the data showed by Colella *et al.* in this issue help cement the importance of telomere biology as a marker of cellular and organismal health.

Conflicts of interest

The authors declare no conflicts of interest.

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