Editorial

Telomerase
Location, Location, Location?

Andreas M. Beyer, Laura E. Norwood Toro

In this issue of *ATVB*, Richardson et al[1] investigate the contribution of telomerase in different cell types within the hematopoietic linage to the development of atherosclerosis. The study raises several interesting points that address an ongoing controversy whether telomere length (TL) is or is not an independent risk factor for development of atherosclerosis and coronary artery disease.

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Telomerase consists of TERT (catalytic subunit) and TERC (RNA component) and is well described as an antiaging factor. The 2009 Nobel Prize in Medicine or Physiology was awarded to Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak for their discoveries on how chromosomes are protected by telomeres and the enzyme telomerase.[2] Although there are numerous substances that claim to elongate telomeres (mostly seen on late-night television), no drug conferring longevity by telomerase has been discovered. In contrast to the beneficial effects of chromosomal elongation to overall cellular and organismal heath, the nuclear actions of telomerase promote cellular immortality, contributing to the progression, but not development, of cancers.[3] Not surprisingly, the role of telomerase activity (TA) and TL is mostly studied in the cancer literature,[4] and TERT inhibition has been explored as a chemotherapeutic. Despite the potential utility of TERT inhibition in cancer, no Food and Drug Administration–approved telomerase inhibitors exist. To further complicate the matter, cellular and subcellular localization seems to contribute to the prevention or increased risk of cancer,[5] cardiovascular disease,[6] defects of the endocrine system,[7] and neurodegenerative disease,[8] to name a few (Figure). In this editorial, we attempt to discuss the growing evidence of tissue-specific and subcellular effects of TA and TL and their role in cardiovascular pathology.

Mice are not men—rodents have longer telomeres compared humans (10- to 100-fold, depending on cell type), and pathologically short telomeres and associated effects are not observed until 3 to 4 generations of intercrossing homozygote knockout mice. Telomerase knockout mice are protected from development of atherosclerosis[9] via a not yet identified mechanism. Neither TERT$^{-/-}$nor TERC$^{-/-}$ mice have obvious signs of cardiovascular disease in early generations, and only in later generations show a progressive increase in systemic blood pressure and large vessel dysfunction.[10,11] In contrast to the progressive telomere shortening that take generations to be observed, our recently published work shows endothelial defects in both mouse[12] and human[13] microvessels that are telomere independent and entirely mediated by TERT. Interestingly, TERC knockout mice have no endothelial phenotype in early generations but develop large vessel defects in later generations, presumably directly related to telomere shortening.[10] Work by the Blasco lab[14] has elegantly demonstrated that short-term overexpression of TERT increases overall survival and decreases infarct size in mouse models of myocardial infarction. This evidence points toward both traditional and nontraditional roles for TERT in contributing to the cardiovascular phenotype(s) observed in relation to telomerase, with TERC only contributing to the traditional role of telomerase.

Decreased TL has been associated with many diseases in small-scale studies, including atherosclerosis and coronary artery disease.[15,16] Recently, several papers suggested that TA, rather than TL, is the important factor associated with disease development/progression.[17–19] Several large-scale studies for coronary artery disease[13] and atherosclerosis[20] have confirmed this. The free-radical theory of aging postulates that aging occurs because of accumulation of free-radical damage over time, providing at least one reason why aging is the number one risk factor of cardiovascular disease. TERT, but not TERC, has been shown to protect against mitochondrial-derived reactive oxygen species and $_{mt}$DNA (mitochondrial DNA) damage[21,22] and is a likely cause of telomere independent contributions to the development of cardiovascular disease. Most studies that link TL to disease development/progression have used peripheral mononuclear blood cells as surrogate markers to study tissue TL and TA. An obvious downfall of this approach is that peripheral mononuclear blood cells consist of several different cell types that contribute differently to the development and prevention of disease. Addressing this point, the data of Richardson et al[1] explore the effects of TL and TA in primary splenocytes sorted into different subpopulations that could contribute to the development of atherosclerosis. Presented data show that telomerase is critical for lymphocyte proliferation but has no role in T_{reg} (regulatory T cell) function if the TL is not critically short. Differences in cellular proliferation during oxidative stress and inflammation (caused by hyperoxia) are because of a specific CD4+ population of T cells but not B cells or monocytes. The reduction in proliferation because of hyperoxia was associated with reduced TA, and pharmacological stimulation of TA stimulated proliferation. Using mouse models, Richardson et al[1] tried to separate out the effects of early loss of telomerase where TL is still similar to wild type

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(*Arterioscler Thromb Vasc Biol*. 2018;38:1247-1249. DOI: 10.1161/ATVBAHA.118.311054.)

***Arterioscler Thromb Vasc Biol* is available at http://atvb.ahajournals.org**
DOI: 10.1161/ATVBAHA.118.311054

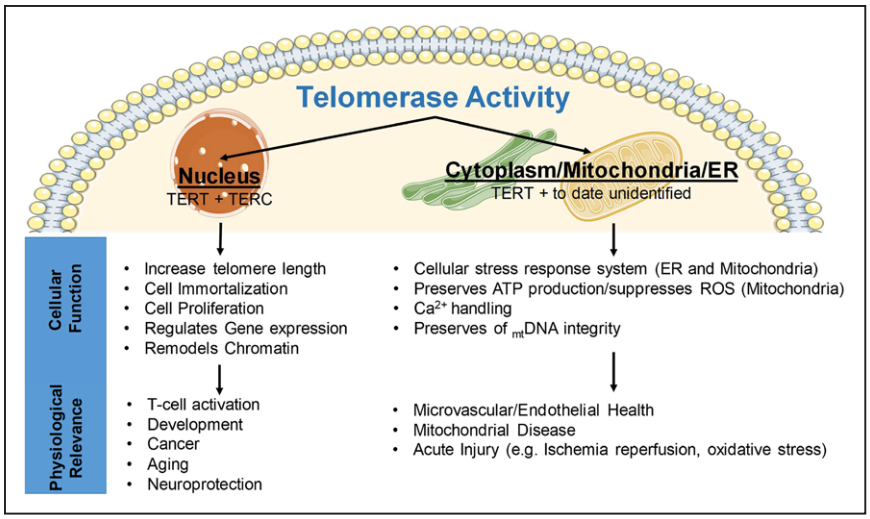

Figure. Subcellular and tissue-specific contribution of telomerase activity to cardiovascular physiology. ER indicates endoplasmic reticulum; and ROS, reactive oxygen species.

(TERT$^{-/-}$, only observed changes in CD4+ T cell proliferation) from later generations that have critically short telomeres (TERC$^{-/-}$ observed proliferation and activity defects in CD4+ T_{reg} cells). However, by not using the same genetic model, the differences in phenotypic changes could be because of differences in TL or differences in noncanonical TERT functions. Although the data support a critical role of TA activity in the proliferative response, the authors also did not directly investigate whether TL was changed in the stressed proliferating splenocytes. In line with the greater developing picture, this evidence suggest that atherosclerosis development is affected by both increase in oxidative stress and acceleration of telomere attrition in T_{regs} via nuclear actions of telomerase.

The complete mechanism of the nontraditional role of TERT has yet to be identified. The work by Richardson et al[1] in this issue suggests the matter is more complex than first meets the eye. With existing evidence, telomerase seems to have highly specific roles in different cell types that contribute to the development of cardiovascular disease, and further work to evaluate contributions of other cell types is warranted and should expand to other diseases. Present evidence supports the notion that increased TA in T cells or endothelial cells can protect against cardiovascular related defects, and small molecule activators, such as TA-65 or AGS-499, deserve consideration as therapeutic interventions.[13,23–25]

Acknowledgments

This work was partially supported by National Institutes of Health grants R01-HL133029 and the Advancing a Healthier Wisconsin Endowment/MCW Redox Biology program (A.M. Beyer). We thank Dr Karima Ait-Aissa for her assistance in generation of the Figure.

Disclosures

None.

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KEY WORDS: Editorials ■ atherosclerosis ■ coronary artery disease ■ mice ■ risk factors ■ telomerase

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2018;38:1247-1249
doi: 10.1161/ATVBAHA.118.311054
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636