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Telomerase – Location, Location, Location?

A. M. Beyer[1,2,3,4] and **L. Norwood Toro**[1,2]

[1]Dep. of Medicine

[2]Cardiovascular Center

[3]Dep. of Physiology

[4]Redox Biology Program

In this issue of ATVB, Richardson and colleagues investigate the contribution of telomerase in different cell types within the hematopoietic linage to the development of atherosclerosis[1]. 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 (CAD).

Telomerase consists of TERT (catalytic subunit) and TERC (RNA component), and is well described as an anti-aging 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]. While 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 in 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 FDA approved telomerase-inhibitors exist. To further complicate the matter, cellular and subcellular localization appear 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. 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 (10–100 fold, depending on cell type), and pathologically short telomeres and associated effects are not observed until 3–4 generations of intercrossing homozygote knock-out mice. Telomerase knock-out 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

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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 knock-out 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 telomere length (TL) has been associated with many diseases in small scale studies, including atherosclerosis and CAD[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 CAD[13] and atherosclerosis[20] have confirmed this. The free-radical theory of aging postulates that aging occurs due to accumulation of free-radical damage over time, providing at least one reason why aging is the number one risk factor of cardiovascular disease (CVD). TERT, but not TERC, has been shown to protect against mitochondrial-derived reactive oxygen species (ROS) and $_{mt}$DNA damage[21,22], and is a likely cause of telomere independent contributions to the development of CVD. Most studies that link TL to disease development/progression have used peripheral mononuclear blood cells (PBMCs) as surrogate markers to study tissue TL and TA. An obvious downfall of this approach is that PBMCs 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, explore the effects of TL and TA in primary splenocytes sorted into different subpopulations that could contribute to the development of atherosclerosis[1]. Presented data shows that telomerase is critical for lymphocyte proliferation but has no role in T_{reg} function if the TL is not critically short. Differences in cellular proliferation during oxidative stress and inflammation (caused by hyperoxia) are due to specific CD4+ population of T cells, but not B cells or monocytes. The reduction in proliferation due to hyperoxia was associated with reduced TA, and pharmacological stimulation of TA stimulated proliferation. Using mouse models, Richardson and colleagues tried to separate out the effects of early loss of telomerase where telomere length is still similar to wild-type ($TERT^{-/-}$, 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 due to differences in telomere length or differences in non-canonical TERT functions. While 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 non-traditional role of TERT has yet to be identified. The work by Richardson et all in this issue[1] suggests the matter is more complex than first meets

the eye. With existing evidence, telomerase appears to have highly specific roles in different cell types that contribute to the development of CVD, and further work to evaluate contributions of other cell types are 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].

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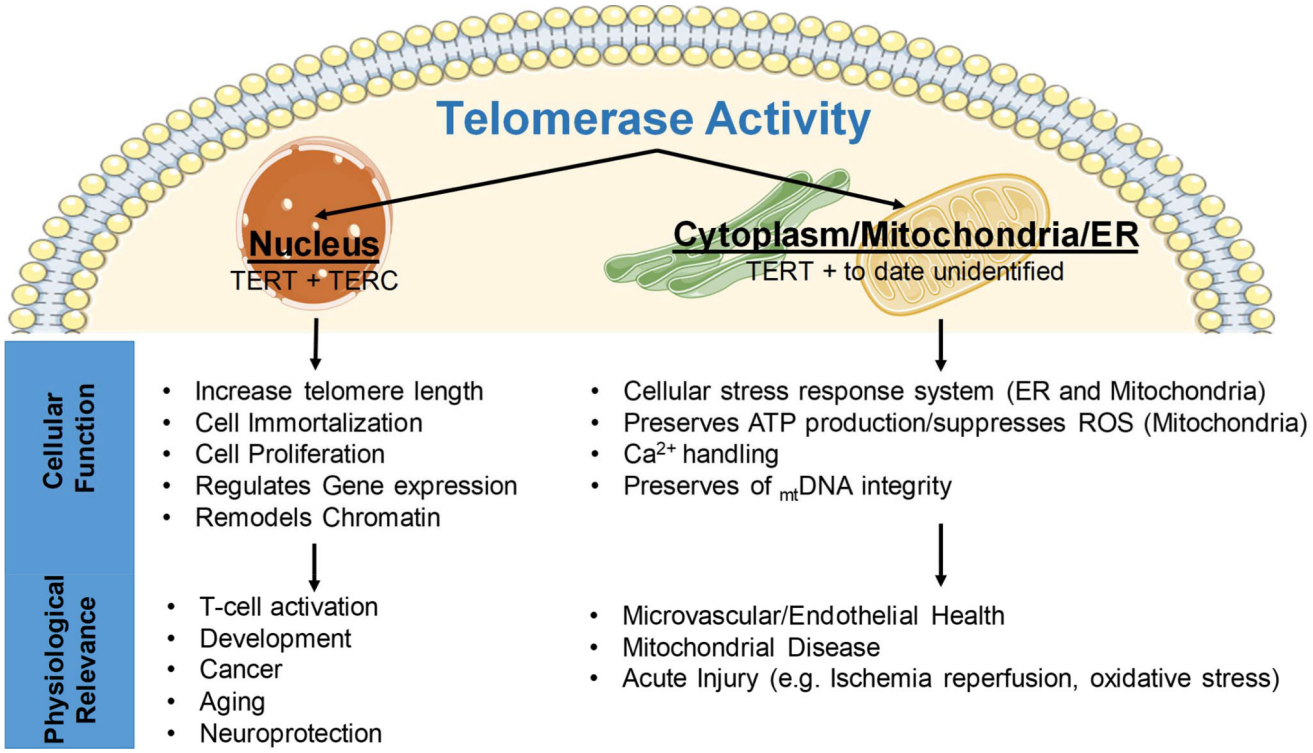

Figure 1.
Subcellular and Tissue Specific Contribution of Telomerase Activity to Cardiovascular Physiology