The Secret Life of Telomerase

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To prevent DNA loss during mitosis, nature has cleverly placed telomeres on the ends of chromosomes to function as disposable nucleotide sequences. Telomeres do, however, shorten with progressive cell division and without a mechanism to compensate; cells are eventually forced into senescence. Telomerase is an essential ribonucleoprotein complex responsible for adding TTAGGG to 3’ ends, and the catalytic subunit at its core is telomerase reverse transcriptase (TERT). Although it is clear that telomerase’s primary function is to prevent the gene truncation, reports of TERT and other complex subunits in mitochondria have fueled speculation of a secret life. That life may entail TERT affecting mitochondrial processes, except during coronary artery disease when vessels switch to H$_2$O$_2$. To assess whether this switch is coupled to TERT and mitochondrial H$_2$O$_2$ production, the authors generated 2 central observations. First, arteries from patients without coronary artery disease experienced a transformation in flow-mediated dilation, a process enabled by nitric oxide species. Reactive oxygen species, such as H$_2$O$_2$, may in turn serve as signaling molecules connecting telomerase activity to a broader spectrum of biological processes.

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In the current issue of *Circulation Research*, Beyer et al7 build on this conceptual thread pursuing a unique line of inquiry in the resistance vasculature. Could telomerase, or more specifically TERT, regulate arterial tone by localizing to mitochondria and influencing the production of reactive oxygen species? The authors make a strategic choice to focus on flow-mediated dilation, a process enabled by nitric oxide production, except during coronary artery disease when vessels switch to H$_2$O$_2$. To assess whether this switch is coupled to TERT and mitochondrial H$_2$O$_2$ production, the authors generated 2 central observations. First, arteries from patients without coronary artery disease experienced a transformation in flow-mediated dilation (nitric oxide to mitochondrial H$_2$O$_2$) if incubated with the telomerase inhibitor, BIBBR-1532. Next, the reverse transformation is clearly demonstrated in arteries harvested from patients with coronary artery disease, exposed to the telomerase activator AGS-499. With the table set, the authors bring TERT closer with the switch in vascular function. They specifically show in intact tissues that (1) TERT is present in vascular cells, (2) TERT expression decreases in patients with coronary artery disease, and (3) telomerase activity is inversely related to mitochondrial H$_2$O$_2$ production. They additionally reveal in cell systems that telomerase activation elevates nitric oxide production and that interfering with the mitochondrial TERT targeting leads to a deleterious rise in superoxide production. From these findings, it is provocatively argued that nonnuclear telomerase activity is biologically important to the maintenance of endothelial function, the production of reactive oxygen species, and the setting of arterial tone (Figure).

In its widest context, the findings of Beyer et al7 are notable in 2 key aspects. First, the authors forwarded a nuanced understanding of the literature to launch a novel hypothesis that ties distinct fields together. Next, instead of relying on animal models, the authors shrewdly exploited variances in human tissue function to garner new insight into TERT’s alternative role in cell function. This was an intriguing twist and one worth recognition given its clear translational significance. Juxtaposed to these strengths are the limitations that come with human work, the most significant being a limited ability to develop strong mechanistic linkages. The authors, for example, could not determine the precise means by which (1) telomerase modulates mitochondrial reactive oxygen species or how (2) TERT translocates from the nucleus. Irrespective of these issues, the observations of Beyer et al are enticing as they raise awareness to the nonnuclear function of telomerase in endothelial cells as a regulator of arterial tone. Is this an end to telomerase’s secret life in the mitochondria or is there another story to be told?

Sources of Funding

This work was supported by an operating grant to Dr Welsh from the Natural Science and Engineering Council of Canada. Dr Welsh is also the Rorabeck Chair in Neuroscience and Vascular Biology at the University of Western Ontario.

Disclosures

None.

References


Key Words: Editorials ■ hydrogen peroxide ■ mitochondria ■ telomerase

Figure. Illustrative diagram highlighting the role of telomerase in flow-induced dilation in human arteries. MLCK indicates myosin light chain kinase; MLCP, myosin light chain phosphatase; mtROS, mitochondrial reactive oxygen species; and TERT, telomerase reverse transcriptase.
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Circ Res. 2016;118:781-782
doi: 10.1161/CIRCRESAHA.116.308290

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