Editorial

Expanding the Concept of Telomere Dysfunction in Cardiovascular Disease

Pim van der Harst, Dirk J. van Veldhuisen, Nilesh J. Samani

Cellular repair and regeneration are considered important features of cardiovascular homeostasis. Exhaustion of these processes and replicative senescence during aging may promote cardiovascular diseases.1 This concept has recently received support from studies that used telomere length as a marker of biological aging and predictor of replicative senescence.1 Further studies show that shorter telomere length, which indicates older cells, is associated with several types of cardiovascular diseases including atherosclerosis2 and heart failure3 (Figure). Most of the studies to date have used white blood cell telomere length as a marker of ageing, but these might not necessarily be the most relevant cells to study.

There is evidence that cells originating from the bone marrow contribute to cardiovascular repair and outcome.4,5 In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology,6 Spyridopoulos et al focus on these cells and expand the evidence for the association between telomere biology and cardiovascular disease. They report a number of novel observations. First, they report a correlation between bone marrow cell telomere length and the number of affected coronary vessels. This is similar to findings made using peripheral white blood cells, and further supports the association between shorter telomeres and coronary artery disease. Second, they demonstrate a correlation between telomere length in bone marrow cells and circulating white blood cells. This is not entirely surprising as these cells originate from the bone marrow. Interestingly, the correlation was stronger with telomere length of granulocytes than those of lymphocytes. This probably reflects the longer life span in the circulation and exposure to environmental factors of lymphocytes and further turnover of these cells compared to granulocytes. Third, and perhaps their most interesting observation is that a functional parameter of bone marrow cells related to telomere length. Specifically, they found that a proportion of the variation (approximately 18%) in migratory capacity of mononuclear bone marrow cells to VEGF was associated with telomere length of lymphocytes and, even somewhat better, the difference between lymphocyte and granulocyte telomere length. Surprisingly, there did not appear to be an independent association of this functional parameter with either bone marrow cell telomere length or with granulocyte telomere length. This seems to be in contrast with previous data from the same group suggesting that both granulocytes and lymphocytes telomere length are associated with colony forming capacity of bone marrow–derived mononuclear cells.7,8 One would have anticipated that the response of bone marrow cells to VEGF would perhaps have been more dependent on the telomere length in the bone marrow cells, themselves. It is therefore unclear how or why the lymphocyte telomere length and the gap between granulocyte and lymphocyte telomere length relates to the migratory capacity of bone marrow cells to VEGF. Nonetheless, they do corroborate the potential relevance of the granulocyte-lymphocyte gap by demonstrating in an independent cohort that this gap is greater in patients with CAD compared with controls.

Limitations

There are some limitations to the current study. For example, the authors used materials obtained from highly selected patients included in a study involving transfusion of progenitor cells to the heart.5 In addition, the authors performed only very basic characterization of the bone marrow and circulating cell potentials. It is therefore unclear whether all bone marrow stem cells, including those with attributed repair functions, have shorter telomeres in patients with CAD. Nonetheless, the additional evidence over and above previous findings is that not only is there an association between telomere length and cardiovascular disease, but that there also appears to be a relationship between telomere length, cell turnover, and bone marrow function which could have important implications for both understanding the mechanisms and identifying potential novel therapeutic targets.

Implications

A current vogue in the field is to use bone marrow cells derived from the patients to enhance repair and preserve left ventricular function after myocardial infarction.5 The present findings, if confirmed in larger studies, suggest that the patients’ bone marrow cells may not be the most optimal to use, unless their dysfunction can be improved. One intriguing option in this regard is the evidence that statins affect telomere biology9 and also that the patients who seem to benefit most from statin treatment clinically are those with the shortest telomeres.2

Currently, an exponential number of studies are being published reporting an increasing number of associations

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between telomere length measurements and cardiovascular diseases or traits. There are also interesting findings from experimental studies which suggest that telomere dysfunction in various cell types could lead to a cardiovascular phenotype. Telomere length is affected by genetic, environmental, and replicative factors (Figure). In this regard, it provides an attractive mechanism to bring together different strands in the etiology of cardiovascular diseases. The study by Spyridopoulos et al provides another layer in the increasing level of evidence linking telomere dysfunction with cardiovascular disease. However, it is still unclear whether the associations represent causal mechanisms or are epiphenomena arising from common factors affecting telomere length and disease.

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**Disclosures**

None.

**References**


**Figure.** A, Telomeres (red) are located on the extreme ends of the chromosome (green). B, Hypothetical effects on BM stem cells, lymphocytes, and granulocytes of known factors determining telomere length, include replicative stress, risk factors (eg, oxidative stress), and the strong genetic determinant. C, The potential levels on which the association between telomere length and the cardiovascular disease continuum (D) may lie. BM indicates bone marrow; WBC, white blood cells; CAD, coronary artery disease; CHF, chronic heart failure.
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