The role of telomeres in maintaining genetic stability was first described by Blackburn in 1991. Telomeres and their associated proteins provide protection against DNA degradation because 40 to 200 bp of the telomere’s tandem repeats are lost on each successive cell division, resulting in the progressive shortening of chromosomes. Telomeres also help to regulate the “cellular clock” because critically short telomeres trigger a cell cycle checkpoint, resulting in replicative senescence (ie, a natural process for terminally differentiated somatic cells, yet undesirable for hematopoietic cells, which require the potential for regulated proliferation throughout life). Thus, exquisite regulation of telomerase is required for extension of telomeres under appropriate conditions in immune cells. Indeed, overexpression or underexpression of telomerase or its reverse transcriptase catalytic domain, human telomerase reverse transcriptase (hTERT), is associated with numerous noncanonical functions of telomerase in biological processes downstream of cytokine stimulation. This finding is in agreement with numerous studies showing that lymphocytes selectively reactivate telomerase in response to environmental activation cues, such as exposure to antigen. In these studies, researchers showed that expression of hTERT is enhanced after stimulation through the B- or T-cell receptors, indicating that, unlike somatic cells, lymphocytes possess the ability to reactivate telomerase when proliferation is required. Although the role of telomerase in myeloid cells is less well characterized, Ping et al recently showed that telomerase activity is increased in primary dendritic cells during differentiation from bone marrow precursor cells. Collectively, these studies indicate that immune cell activation can induce expression and activity of telomerase.

Atherosclerotic lesions, which are considered to be the single most important contributor to cardiovascular disease, are characterized by tissue-resident macrophages that propagate local inflammation and tissue destruction through the production of reactive oxygen intermediates, proinflammatory cytokines, and matrix metalloproteinases that degrade and remodel the extracellular matrix. Given the impact of telomere dysregulation on the fundamental cellular processes involved in inflammation, and the dearth of knowledge regarding telomerase activity in myeloid cells, the potential role for telomerase in mediating macrophage dysfunction is an important research area.

Recent work has begun to unravel this question in the context of atherosclerosis. In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Gizard et al show that expression of hTERT and functional activity of telomerase are induced in primary macrophages after proinflammatory signaling (Figure). This finding is in agreement with numerous studies showing that lymphocytes selectively reactivate telomerase in response to environmental activation cues, such as exposure to antigen. In these studies, researchers showed that expression of hTERT is enhanced after stimulation through the B- or T-cell receptors, indicating that, unlike somatic cells, lymphocytes possess the ability to reactivate telomerase when proliferation is required. Although the role of telomerase in myeloid cells is less well characterized, Ping et al recently showed that telomerase activity is increased in primary dendritic cells during differentiation from bone marrow precursor cells. Collectively, these studies indicate that immune cell activation can induce expression and activity of telomerase.

Immune cell proliferation can be initiated through signaling events downstream of proinflammatory stimuli, such as oxidized low-density lipoprotein, lipopolysaccharide, and tumor necrosis factor α, that converge in gene expression pathways, including nuclear factor (NF)-κB. In their current article, Gizard et al explore the link between inflammation and elevated telomerase activity in macrophages after cytokine and oxidized low-density lipoprotein signaling. Their work identifies a novel NF-κB response element in the TERT promoter, demonstrating that TERT is an NF-κB target gene and suggesting that telomerase activity can be transcriptionally regulated after cytokine stimulation. In addition, previous work from Akiyama et al showed that NF-κB regulates telomerase activity posttranslationally because it mediates hTERT nuclear translocation through a physical association. Together, the work of Gizard and Akiyama and colleagues highlights the complexity of telomerase regulation through both transcriptional and posttranslational mechanisms downstream of cytokine stimulation.
Many inflammatory diseases, including atherosclerosis, are associated with aging. Because aging also correlates with telomere shortening, lowered telomerase activity has been hypothesized to play a causal role in the development of atherosclerosis and cardiovascular disease. Findeisen et al7 suggest that the role of telomerase may not be so straightforward; they recently showed that TERT deficiency in bone marrow cells is protective against the formation of abdominal aortic aneurysm in mice. Interestingly, protection against aneurysm was associated with lowered matrix metalloproteinase production by macrophages. Furthermore, Gizard et al8 demonstrate that TERT is strongly expressed in human coronary artery atherosclerotic lesions and that TERT expression colocalizes with the macrophage marker CD68. Development of atherosclerotic lesions in low-density lipoprotein receptor−/− mice receiving a high-fat diet also correlated with increased telomerase activity, further implicating elevated TERT and telomerase activity with the development of atherosclerosis.

Perhaps not surprisingly, the role of telomerase in inflammation remains a complex issue. Recent work from Bhattacharjee et al14 has shown that mice lacking TERC, the RNA template for telomerase transcriptional activity, express elevated levels of toll-like receptor 4 and are prone to inflammation. Although these findings may seem contradictory to those of Gizard et al,8 they raise the possibility that certain telomerase activities may remain intact in mice lacking TERC. Although these noncanonical telomerase functions may not directly involve reverse transcriptase activity, another recent study from Poch et al15 showed that shortened telomeres are protective against diet-induced atherosclerosis in apolipoprotein E−/− mice. Thus, noncanonical activities of TERT may not be totally disconnected from traditional effects on telomeres.

The modulation of telomerase activity represents an attractive therapeutic strategy for numerous diseases, and inhibition of TERT has already been successfully translated to anticancer therapies.16 Conversely, reactivation of telomerase was recently shown by Jaskelioff et al17 to reverse systemic degenerative disease in aged mice. Whether similar therapeutic strategies will prove useful in the treatment of chronic inflammatory diseases, such as atherosclerosis, remains unknown. Nevertheless, the work of Gizard et al8 marks an important step toward unraveling the complex role of TERT in inflammatory diseases.

Disclosures

None.

References

Length Does Not Matter: A New Take on Telomerase Reverse Transcriptase
Wendy A. Goodman and Mukesh K. Jain

_Arterioscler Thromb Vasc Biol._ 2011;31:235-236
doi: 10.1161/ATVBAHA.110.220343

_Arteriosclerosis, Thrombosis, and Vascular Biology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/31/2/235