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Editorial Commentary

Leukocyte Telomere Length, Hypertension, and Atherosclerosis

Are There Potential Mechanistic Explanations?

Abraham Aviv

In this issue of *Hypertension*, Yang et al[1] report that leukocyte telomere length (LTL) is shorter in hypertensive patients than in their normotensive peers. What's more, after 5 years of follow-up, the authors observed that hypertensive patients with short LTL were more likely to develop atherosclerotic coronary artery disease, whereas normotensive persons with short LTL were more likely to become hypertensive.

Several features of this study merit attention. First, the study was conducted in a Chinese cohort, whereas the information we have about the relationships between LTL and cardiovascular risks is primarily derived from white populations. Second, the size of the cohort (388 hypertensive and 379 normotensive persons) and the meticulous attention devoted to characterizing hypertension lend credibility to the findings. Third, the 5-year follow-up period provided the opportunity to explore the potential cardiovascular ramifications of having a short LTL. Thus, the findings of this work indicate that the association between LTL and risks for coronary artery atherosclerosis apply not only to white but also to Chinese populations.

What is the biological meaning of the associations between LTL and aging-related diseases, principally atherosclerosis and its risk factors? The short answer is: we do not know. What we do know is that LTL is highly variable at birth and throughout life.[2] We also know that age-dependent LTL shortening is much faster in early life than during adulthood,[3] probably because of the rapid proliferation of hematopoietic stem cells (HSCs) during growth and development. In fact, LTL shortening throughout life largely mirrors telomere shortening in HSCs. In these cells, like in other somatic cells with rudimentary activity of telomerase (the reverse transcriptase that adds telomere repeats onto the ends of chromosomes), telomere shortening records replication.[4] So what does replication of HSCs have to do with hypertension, aging, and cardiovascular aging in particular? Presently, this is the most fundamental and pressing question in telomere epidemiology.

Studies in cultured somatic cells have revealed that cell replication is the ultimate cause of telomere shortening. As these cells undergo division, their chromosomal ends, which are composed of thousands of TTAGGG repeats, progressively shorten because of the inability of DNA polymerase to replicate the lagging DNA strand to its terminus, a phenomenon coined the "end-replication problem." However, oxidative stress exerts major influence on telomere shortening over and above that of the end-replication problem because, evidently, the GGG triplets on the telomeres are highly sensitive to the hydroxyl radical. Thus, increased oxidative stress somehow results in a longer stretch of telomeres being lost with each cell replication.[5] In this sense, telomere dynamics, ie, telomere length and its shortening, is a record of not only the replicative history but also the accruing burden of oxidative stress of cell populations that undergo replication. However, telomere dynamics has an additional feature that is highly relevant to all of the epidemiological studies that link LTL with aging-related diseases: as telomere length becomes critically shortened, the cellular replicative machinery stops functioning, which usually leads to replicative senescence. Under most circumstances, replicative senescence is an irreversible cellular state.

Assuming that what applies to somatic cells in culture also applies to HSCs in vivo, what might be the biological meaning of a relatively short LTL? At any age, short LTL is the result of short telomere length of HSCs at birth, a relatively high rate of telomere shortening in these cells afterward, or both. Because telomere length is highly variable at birth, everything else being equal, individuals endowed with relatively long LTL at birth are more likely to display at any age a longer LTL than those born with a short LTL. However, hardly anything is equal among humans, which also applies to the rate of LTL shortening after birth, a process that is as variable as birth LTL.[6]

HSC replication serves to maintain the numbers and functions of all of the circulating blood cells, a mechanism that accounts first and foremost for age-dependent LTL shortening and, evidently, its acceleration in inflammatory states. Regardless of its etiology, chronic inflammation entails an increase in the numbers of leukocytes in the circulation and in their heightened expenditure. The demands to maintain the numbers of these cells would promote an increase in the replication of cells up the hierarchy of the hematopoietic system, which ultimately involve the HSCs. Thus, from the standpoint of the hematopoietic system,

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chronic inflammation entails an increase in the rate of HSC replication, an increase in the turnover of leukocytes, and a shorter LTL.

Systemic oxidative stress is another factor that might enhance the rate of telomere shortening in HSCs. As per its impact on cultured cells, oxidative stress probably augments telomere shortening per the replication of HSCs and perhaps a subset of peripheral leukocytes, ie, lymphocytes, which replicate in the circulation. In this way, oxidative stress is presumed to accelerate LTL shortening in 2 ways: by increasing telomere loss in HSCs and by diminishing the biological life of a subset of peripheral leukocytes, which would further enhance HSC replication to accommodate peripheral needs.

Indicators of inflammation and oxidative stress in the blood reflect the metabolic status at the moment of sample collection. In contrast, LTL is ostensibly a record of the cumulative burden of inflammation and oxidative stress over the individual's life span. Because inflammation and oxidative stress are at the center of hypotheses that attempt to make sense of the aging process, the unique feature of LTL as a record of the cumulative burden of inflammation and oxidative stress might explain its association with aging-related diseases and particularly atherosclerosis.

Atherosclerosis is an aging-related systemic disease that is driven in large measure by inflammation and oxidative stress, low grade and chronic.[7,8] Accordingly, the shortened LTL that is often observed in patients who suffer from atherosclerosis or display risks, including hypertension, for this disorder might reflect a higher accruing burden of inflammation and oxidative stress on the hematopoietic system. From this standpoint, shortened LTL, and, by implication, telomere length in HSCs, are just biomarkers of the atherosclerotic process. However, as aptly pointed out by Yang et al,[1] recent studies suggest an intriguing alternative, namely, that LTL might somehow relate to the function of endothelial progenitor cells. Thus, shortened LTL might be an index of reduced HSC reserves, expressed in a limited ability of the bone marrow to supply adequately functioning endothelial progenitor cells.

The development of most diseases is the outcome of an imbalance between injurious factors and elements that serve to counter their effects. Endothelial progenitor cells originate from the HSC pool and possess the unique ability of homing to sites of injured endothelium, where they integrate themselves into the vascular wall and engage in endothelial repair.[9] Atherosclerosis, a disease that apparently starts with endothelial injury, is marked by diminished numbers of endothelial progenitor cells in the circulation and reduced function of these cells, a flaw that might arise from shortened telomere length.[10]

Viewing LTL from the perspective of HSC dynamics shows that the relationships of LTL with atherosclerosis and its risks, hypertension included, might not neatly fit into a single mechanistic scheme. LTL, like hypertension, atherosclerosis, and other aging-related diseases, is a complex genetic trait. Each individual is dealt a different hand of traits that ultimately determine susceptibility to these diseases. In some individuals, susceptibility to atherosclerosis might reflect relatively low HSC reserves at birth. In others, these reserves might be depleted at a faster pace after birth by a variety of genetic and environmental factors. Either way, shortened LTL during adulthood appears to serve as a general, albeit imperfect, biomarker of the lifetime risk of atherosclerosis and other related diseases. That being said, shortened telomere length at the level of HSCs could also be a determinant in the development of these diseases. Accordingly, a tall task of human telomere research is to figure out which of the 2 major ingredients of LTL, that is, birth LTL or its shortening thereafter, is a better predictor of the lifetime susceptibility to hypertension and atherosclerosis. An even taller task is to decipher the genes that account for the interindividual variation of LTL among humans.

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Disclosures

None.

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