

Leukocyte telomere length: the telomere tale continues^{1–3}

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In culture, replicating human somatic cells display progressive telomere shortening. Ultimately, such cells either undergo apoptosis or enter a state of replicative senescence that is triggered by critically shortened telomeres. Accordingly, telomere length is an index of both the replicative history and the replicative potential of human somatic cells in culture (1).

Most replicating human somatic cells undergo telomere shortening in vivo. In addition, leukocyte telomere length (LTL) is associated with aging-related disorders, principally atherosclerosis (2). Although conflicting results had been published on whether LTL forecasts survival in the elderly, recent research, which used the powerful same-sex twin model, clearly showed that the co-twins with the shorter LTL were more likely to die first (3, 4). These observations support the proposition that LTL is a biomarker of human aging.

Telomeres are a “mitotic clock” in cultured human somatic cells. But many authors, including Xu et al (5), whose article appears in this issue of the Journal (5), refer to telomere length in general as a “marker” of biological aging. That clearly is not the case. Telomere biology in 2 cell types would suffice to illustrate the problem with this generalization. In skeletal muscle, which is largely a postmitotic tissue, telomeres undergo little shortening with age. In hepatocytes, which do replicate, telomere length shortens with age, and cirrhotic livers display relatively shortened telomeres. However, in contrast to LTL, shortened telomeres in liver cells, in health or disease, do not account for the overall (systemic) aging of the individual.

LTL is ostensibly a biomarker of human aging because its dynamics, which are defined by birth LTL and its age-dependent shortening afterward, are apparently fashioned by factors that play a part in the biology of aging. LTL dynamics mirror telomere dynamics in hematopoietic stem cells (HSCs), which are the precursors of the hierarchy of cells that comprise the hematopoietic system (**Figure 1**) (6). HSCs lack sufficient telomerase activity to prevent telomere shortening engendered by their replications—a phenomenon that is ultimately expressed in age-dependent LTL attrition. Telomere length is not identical in subsets of leukocytes, and the numbers of cells belonging to these subsets may change with age. However, variations in LTL among individuals are far larger than those among subsets of leukocytes within the individual. Thus, for each individual, LTL is determined by telomere length of HSCs at birth and its age-dependent shortening over the individual's life span.

LTL is heritable but modified by a host of environmental variables. Cigarette smokers, obese and sedentary individuals, and those with unhealthy habits in general often exhibit not only increases in the systemic burden of oxidative stress and inflammation but also shortened LTL. Telomeres are highly sensitive to the hydroxyl radical, which causes DNA breakage (7). Consequently, increased free radical concentrations might cause the clipping of greater stretches of telomeres with each replication of HSCs. Inflammation would increase the rate of HSC replication to accommodate the increased demand for leukocytes due to their engagement in the inflammatory process. In short, a chronic increase in the systemic burden of oxidative stress and inflammation enhances the rate of telomere shortening in HSCs, which is ultimately expressed in shortened LTL.

Therein lies a potential clue for the findings by Xu et al (5), who observed in a cross-sectional study that LTL (measured by quantitative polymerase chain reaction) was longer in women who reported habitual intake of multivitamin supplements. In addition, women with higher intakes of vitamins C and E, which were estimated on the basis of food intake questionnaires, also showed a longer LTL.

Although the authors attempted to disentangle the effect of self-reported vitamin consumption from that of lifestyle, it is difficult to do so in cross-sectional studies. The Achilles heel of many studies ascribing health benefits to single- or multivitamin intake in the general population was their cross-sectional design. Individuals who consume vitamin supplements and eat vitamin-rich food are more likely to follow a healthy way of living. Indeed, the multivitamin users in the Sister Study smoked less, had a lower BMI, were more educated, and were physically more active than nonusers. Thus, to replicate the findings linking LTL with vitamin intake (5), future work must focus on cohorts that are not only more representative of the general population

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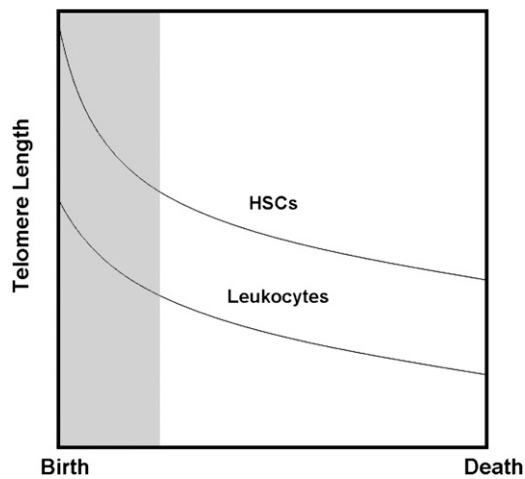


FIGURE 1. Telomere dynamics in leukocytes mirror telomere dynamics in hematopoietic stem cells (HSCs). Shaded area denotes growth period. Rapid telomere shortening during growth is probably due to a high rate of HSC replications that drive the expansions of the HSC pool, the progenitor cell pool, and blood volume in tandem with somatic growth (6).

than the Sister Study cohort but also address the confounding by lifestyle. The latter might be a considerable challenge.

Setting aside the potential lifestyle effect, let's assume that the habitual intake of multivitamins and consumption of supplements of vitamins E and C, which are purported to exert an antioxidant influence *in vivo*, affected LTL. Telomere length of HSCs at birth cannot explain the vitamin-LTL nexus, unless we invoke the unlikely possibility that individuals born with long telomeres in HSCs are prone to ingest multivitamins during adult life. It follows that the habitual ingestion of multivitamins somehow "slows down" the rate of age-dependent telomere shortening in HSCs. On the basis of theoretical considerations, the reduction in systemic burdens of oxidative stress, inflammation, or both might exert such an effect, although the notion that vitamin supplements are able to accomplish such a reduction will surely generate a provocative debate.

However, buried in the results of the study by Xu et al (5) is a finding that might provide compelling evidence linking LTL (HSC) dynamics with oxidative stress *in vivo*. The authors indicate almost in passing that "iron users ($n = 41$) had a shorter telomere length than nonusers ($n = 527$): 5121 ± 183 compared with 5583 ± 87 bp (9.0% difference; $P = 0.007$)." If true and confirmed in cohorts that are more representative of the general population, this might turn out to be the most important observation in the work by Xu et al.

Free iron is a key element in Herber-Weiss and Fenton reactions that generate hydrogen peroxide and hydroxyl radicals. Oral iron supplements given to human volunteers increased the fecal excretion of free radicals, which were presumably generated through these reactions by unabsorbed iron in the colon (8). Can conditions and concentrations of free iron in other organs and tissues of individuals with increased iron loads due to iron supplements generate free radicals via similar mechanisms? We really do not know. Hepatotoxicity is the hallmark of patients who suffer from iron overload due to diseases such as hereditary hemochromatosis and in those who receive repeated blood transfusions due to hemoglobinopathies. A number of studies have implicated increased systemic iron burdens in coronary heart disease. However, findings based on the National Health and Nutrition Examination Survey II (9) and a meta-analysis (10) showed no relation of indexes of iron status (serum ferritin and transferrin saturation) with coronary heart disease and mortality. But perhaps these indexes do not tell the whole story of the consequences of increased systemic iron burden.

In light of the (preliminary) findings of Xu et al, the potential effects of dietary iron supplements on the systemic burden of oxidative stress and LTL dynamics provide an important new target for future studies.

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