Chronology Versus Biology
Telomeres, Essential Hypertension, and Vascular Aging

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Abstract—There is considerable evidence that essential hypertension is closely linked to the growth, development, and aging of human beings. It is imperative, therefore, to introduce biological indicators of growth and aging into models developed to provide a better understanding of the etiology of essential hypertension. One of these indicators may well be the age-dependent telomere attrition rate in somatic cells. Telomere attrition registers the replicative history of somatic cells. As such, it chronicles not only the growth that results from the replication of somatic cells but also their turnover—a process that is strongly linked to inflammation and oxidative stress, which are key factors in the biology of human aging. (Hypertension. 2002;40: 1111–1116.)

Key Words: hypertension, essential ■ aging ■ genetics ■ oxidative stress ■ cardiovascular diseases

Genetic Information, Biological Meaning, and the Limits of Present Models of Essential Hypertension

The search for the causes of essential hypertension has recently produced a stream of reports about variant genes that may raise blood pressure in humans, yet only modest understanding has been gained about the genetic determinants of this complex human trait. For all their power and sophistication, molecular biology and computational genomics will be less helpful in elucidating the causes of essential hypertension if models constructed to explain this disorder are incomplete. Regardless of the question of what constitutes a gene, it is one thing to understand what a gene does; it is quite another to figure out the ultimate role of the gene in the broader context of the organism. This was clearly articulated by E.F. Keller, who states, “Recent developments in molecular biology have given us a new appreciation of the magnitude of the gap between genetic information and biological meaning.”1

When attempts are made to model the functional relevance of a gene by extrapolating from the cellular to the systemic levels, often the most obvious predictions turn out to be incorrect. The experience with “knockout” mice clearly illustrates this point.2 Disabling a specific gene in a mouse does not always result in a living mouse that exhibits the anticipated phenotype based on a priori knowledge of gene function. Misunderstanding about the functions of the targeted gene only partially explains the failure to generate the anticipated phenotype. More often the unanticipated outcome relates to insufficient appreciation of the paramount effect of the biological milieu within which the targeted gene gives rise to phenotypic expressions. This is particularly applicable to complex genetic traits, which generally reflect the input of several or many genes that often interact, not only among themselves and with other genes, but also with the environment.

Primary hypertension is classified as monogenic hypertension or essential hypertension. Monogenic forms of hypertension result from major gene mutations that primarily influence one biological system.3 Each one of these mutations wreaks such physiological havoc that it overrides the actions of environmental factors. Further, when one of these mutations is present, attempts by the body to maintain homeostasis are not fully effective, and they take place at the expense of blood pressure elevation. The resulting well-defined phenotype, which is the signature of the disease, can be readily traced to the mutant gene. For instance, Liddle’s syndrome, arising from excess sodium reabsorption caused by mutations in subunits of the amiloride-sensitive sodium channel in the renal tubules, usually presents as a severe form of hypertension associated with a low plasma renin activity and hypokalemia.4,5

Although essential hypertension has a genetic component,6 it presents with an array of poorly defined phenotypes, apparently arising from multiple variant genes. The difficulties in identifying these variant genes in the general population have been attributed to the polygenic nature of essential hypertension and to the possibility that its phenotypes are poorly defined because of gene-gene and gene-environment interactions. In other words, any variant gene predisposing to essential hypertension would be difficult to identify because its effect on the overall increase in systemic blood pressure is relatively small and obscured by effects of other genes and the environment. What this argument fails to acknowledge, however, is that in industrialized societies, the systemic blood pressure...
pressure—particularly the systolic blood pressure—is largely age-dependent and primarily an index of vascular aging.7–11 In this regard, the search for variant genes that cause human diseases is based on the premise that gene segregation in a population follows principles of evolution by natural selection. But such principles are applicable only during the reproductive years, whereas essential hypertension, and particularly systolic hypertension, primarily occurs during the postreproductive period. It is necessary, therefore, to incorporate the factor of age (aging) into models of essential hypertension. The question that follows is “What type of age indicator should be included in such models?”

Chronology Versus Biology of Aging and Diseases of Aging

Chronological age is an extrinsic entity based on constant calendar units. As a concept and a mainstay of clinical practice, chronological age reflects the premise that aging proceeds at an identical pace for all human beings. Biological age, in contrast, is an intrinsic entity, unique for every organism in that it has been molded by millions of years of evolution by natural selection. Biological age is expressed by the different maximum life spans found among species and by the variations in longevity within members of the same species. For instance, in advanced nations, women live longer than men and a pronounced gender effect is observed in a host of age-related diseases, suggesting that the pace of biologic aging differs between women and men. Because humans are the product of evolution, whereas the calendar is not, one can propose that some indicator of biologic age, rather than chronologic age, might be more applicable to models of human aging, including age-related disorders such as essential hypertension, non–insulin-dependent diabetes mellitus, atherosclerosis, and cancer. The links between essential hypertension, diabetes mellitus, and atherosclerosis are well established, but recently common pathways, at the molecular level, also have been proposed for atherosclerosis and cancer.13 These links underscore the need for biological indicators of aging in evaluating the etiology of these age-related disorders. The criteria proposed for an ideal biomarker of aging include correlation with age in cross-sectional analysis of a population, a longitudinal change with age that follows the direction of the cross-sectional analysis, and stability of individual differences.13 One more criterion for a biologic indicator in the context of models of essential hypertension would be the ability of the indicator to provide an account, in addition to chronologic age, of the age-dependent rise in systolic (pulse) pressure.7–11 Recent studies suggest that telomere length, as expressed in white blood cells, meets these criteria.14,15

Telomeres and Aging In Vitro and In Vivo

Telomeres compriseTTAGGG tandem repeats at the ends of mammalian chromosomes. Together with telomere binding proteins, telomeres protect subtelomeric regions from erosion and prevent associations between chromosomal ends—a phenomenon marked by genomic instability. In cultured somatic cells from humans, telomeres undergo attrition with each cycle of cellular replication until a critical telomere length is attained, at which point cells experience replicative senescence (reviewed in Harley et al16 and in Aviv and Harley17). Telomere length in these cells is, hence, not only an index of replicative history, but also a key determinant of replicative senescence. Support for this idea has been derived from complementary lines of inquiry. First, cancer cells, germline cells, and immortalized cell lines usually express robust activity of telomerase, a reverse transcriptase that adds back the TTAGGG tandem repeats onto the ends of the telomeres.18,19 These types of cell continue to proliferate without evidence of replicative senescence and telomere erosion. Second, the ectopic expression of the catalytic subunit of telomerase in somatic cells expressing little or no telomerase activity results in the phenotypic transformation of these cells, marked by an increase in replicative capacity in some cell types and immortalization in others.20,21 Third, the inhibition of telomerase prevents the continuous growth of cancerous cells.22,23 It is noteworthy, however, that the central role of telomeric erosion in replicative senescence has been shown primarily in cultured somatic cells derived from primates.16,17,24 Mechanisms independent of telomere attrition are responsible for replicative senescence of rodent cells.25 In addition, there is evidence that telomere erosion in cultured human somatic cells may alter through positional effect the expression of genes before the induction of replicative senescence.26

There is no compelling evidence at present that in humans a causal relationship exists in vivo between telomere length and biological aging at the cellular or systemic levels. The lack of such evidence reflects the constrained nature of the in vivo studies, which in humans can primarily yield associative data. The missing evidence for mechanistic causality between telomere biology and human aging does not invalidate the use of telomere length as an indicator of biologic age in paradigms of essential hypertension, given that telomere length explains, in addition to chronological age, pulse pressure variation and the predilection to coronary heart disease among humans.14,15,27 It is possible, for instance, that telomere length is a surrogate marker for the effect of genetic and environmental factors that are determinants of biologic aging. Chief among these factors are reactive oxygen species (ROS).

ROS, Inflammation, Telomere Dynamics, and Pulse Pressure

Oxidative stress is at the center of the free radical theory of aging, which proposes that degenerative senescence is largely the result of the cumulative effect of oxidative end products.28,29 Recent studies have underscored the roles of ROS in the development of vascular pathobiology that is characteristic of age-related disorders such as hypertension and atherosclerosis.30–33 One fact that, thus far, has not received due notice in the medical and research communities is the evidence that ROS are among the few factors that accelerate the rate of telomere attrition in different cell types, including vascular endothelial cells.34,35 There is also some evidence, based on in vitro experiments, that telomere-mediated senescence of vascular endothelial cells may result in endothelial dysfunction, particularly in atherosclerotic regions.36
Inflammation is manifested by an increase in oxidative stress and in the turnover of white blood cells, a process that would accelerate the rate of telomere attrition in these cells. Interestingly, levels of ROS products are lower in women than men,\textsuperscript{57} perhaps because of the ability of estrogen to curtail ROS production and enhance ROS scavenging and degradation.\textsuperscript{38–41} Moreover, women have longer telomeres in white blood cells than men\textsuperscript{14,15}—a finding consistent with lower ROS levels in women than men. Thus, the lasting effect of ROS and inflammation on telomere dynamics in white blood cells, on the one hand, and vascular biology, on the other, may be the missing link between the age-dependent rise in pulse pressure and telomere attrition in white blood cells. In fact, the recent finding of an association between the level of C-reactive protein, a major indicator of inflammation, and pulse pressure\textsuperscript{42} is in line with the concept that inflammation is a major factor that underlies the increased cardiovascular disease risks associated with aging.\textsuperscript{43,44}

### Conclusion

For all we know, telomere length is but one of a number of biologic indicators that may serve to gauge the progression of biologic aging in humans. Although the effect of ROS on biologic tissues is universal, various cells manifest the cumulative damage of oxidative end products differently. For instance, whereas telomere dynamics in white blood cells may chronicle their cumulative oxidative burden through their replicative history, telomere length in the poorly proliferating skeletal muscle cells and nerve cells is unlikely to register the effect of ROS, because telomere erosion only occurs with somatic cell division. However, the biological meaning of the variations in telomere length among individuals during intra- and extra-uterine life\textsuperscript{14,15,45–48} remains an enigma. So, even if we understand telomere biology in each organ system at the cellular and molecular levels, we may still need to bridge the gap between this basic understanding and the fact that humans express considerable variability in telomere length. By elucidating the genetic and environmental reasons for this variability, we will be in a better position to substitute biology for chronology, not only in models of essential hypertension, but also in other descriptions of age-related disorders.

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### References

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