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Telomeres and Telomerase in the Fetal Origins of Cardiovascular Disease: A Review

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Abstract

Telomeres are noncoding functional DNA repeat sequences at the ends of chromosomes that decrease in length by a predictable amount at each cell division. When the telomeres become critically short, the cell is no longer able to replicate and enters cellular senescence. Recent work has shown that within individuals, telomere length tracks with cardiovascular health and aging and is also affected by growth variation, both prenatally and postnatally. Therefore telomere length can be a marker of both growth history (cell division) and tissue function (senescence). Relationships between early growth and later health have emerged as a research focus in the epidemiology of chronic diseases of aging, such as heart disease and diabetes. The “fetal origins” literature has demonstrated that hormonal and nutritional aspects of the intrauterine environment not only affect fetal growth but also can permanently alter the metabolic program of the individual. Smaller infants tend to have a higher risk of developing cardiovascular disease. Much less attention has been paid to possible genetic links between the processes of early growth and later disease. Our aim in this review is to summarize evidence for one such genetic mechanism, telomere attrition, that may underlie the fetal origins of cardiovascular disease and to discuss this mechanism in light of the evolution of senescence.

Keywords

FETAL GROWTH RETARDATION; GROWTH; BIRTH WEIGHT; AGING; REPLICATIVE SENESCENCE; TELOMERE; TELOMERE ATTRITION; TELOMERASE; ANTAGONISTIC PLEIOTROPY; MUTATION ACCUMULATION; EVOLUTION; HEART DISEASE; ARTERIOSCLEROSIS; HYPERTENSION; EPIDEMIOLOGY

Complex cardiovascular and metabolic diseases of middle and old age, including hypertension, dyslipidemia, non-insulin-dependent diabetes mellitus (NIDDM), and atherosclerosis traditionally have been considered the result of behavioral risk factors in adulthood (e.g., smoking, obesity, poor diet, and inactivity) interacting with genetic predispositions to disease. In the last decade this paradigm has been confronted by studies that point to nutritional status during prenatal life as a critical determinant of the risk of these diseases. Following the initial finding by David Barker and colleagues of an association between the prevalence of low birth weight and the rate of death resulting from heart disease in the United Kingdom (Barker et al. 1993, 1989), the “fetal origins” literature has revealed that relatively small variations in birth weight and other markers of fetal growth

are consistent, if unexpected, correlates of blood pressure (Barker et al. 1989; Curhan, Chertow et al. 1996; Curhan, Willett et al. 1996; Fall et al. 1995; Hales et al. 1991; Kolacek et al. 1993; Rich-Edwards et al. 1997; Whincup et al. 1992), cholesterol concentration (Barker et al. 1993), carotid atherosclerosis (Martyn et al. 1998), fibrinogen (Martyn et al. 1995), and the metabolic syndrome (Curhan, Willett et al. 1996; Hofman et al. 1997; Lithell et al. 1996; Ong et al. 1999; Rossing et al. 1995; Silverman et al. 1998; Stern et al. 2000) in adult life. Further research has elaborated on these findings to show that accelerated or particularly rapid growth during early life, usually in combination with restricted fetal growth, poses risks to adult health (Crowther et al. 1998, 2000; Eriksson et al. 1999, 2001, 2002; Huxley et al. 2000; Law et al. 2002; Mortaz et al. 2001), possibly through greater risk of obesity (Stettler et al. 2002, 2003).

A number of physiologic mechanisms have been proposed to explain these somewhat unexpected findings, including alterations in the fetal hypothalamic–pituitary–adrenal axis, which lead to heightened stress reactivity and reduced insulin sensitivity (Edwards et al. 2001; McTernan et al. 2001; Munck et al. 1984; Reynolds and Phillips 1998; Seckl 1997; Seckl et al. 2000), and reduction in the number of glomeruli in the kidney, which leads to hypertension (Brenner and Chertow 1993; Brenner et al. 1988; Hinchliffe et al. 1992; Konje et al. 1996; Lampl et al. 2002; Lane et al. 1998; Manalich et al. 2000; McKenzie et al. 1996; Paivansalo et al. 1998; Raman et al. 1998; Woods et al. 2001). A review of these studies can be found in a paper by Cameron and Demerath (2002).

Interestingly, most of the fetal origins literature casts growth itself as a side issue—as an indicator, or shared consequence, of the hormonal and nutritional stressors that ultimately cause or program the metabolic derangements that lead to disease. Although the idea that growth, maturation, and diseases of aging are intimately linked to one another is somewhat novel in the field of chronic disease epidemiology, evolutionary biologists have long recognized their intrinsic connections. Both the pace of growth and development and longevity can be viewed as components of a life history program that has been shaped by natural selection to optimize reproductive success. The pattern of human growth is based on a general primate model of rapid brain growth and delayed sexual maturation, allowing for extensive social learning (Bogin 1999; Laird 1967). However, both sexual maturation and the completion of physical growth are particularly delayed in humans compared to other primate species, and both are completed in a rapid adolescent growth spurt (Bogin 1994; Leigh 1996). Humans are also exceptionally long-lived, even compared to other primates, living approximately twice as long as chimpanzees (Kaplan and Robson 2002). Although most of our additional years of life are postreproductive, our longevity still confers reproductive benefits, perhaps by allowing increased social support and “grandmothering” of offspring (Hawkes et al. 1998). Such evolutionary links between patterns of growth and aging suggest that genetic mechanisms might also be involved in the association between fetal and infant growth and cardiovascular senescence.

A relatively new area of research concerns the control of replicative senescence, that is, the arrest of cell division in a cell line, through a molecular clock that counts the number of replications that have occurred in the life of the cell. Telomeres, the repetitive base-pair sequences at the tips of the chromosomes, become shortened in a predictable manner as the result of cell division (growth) and thus constitute this counting mechanism. Because telomeres are protected from shortening by continued telomerase activity in tumor cells, research on telomeres and telomerase has focused strongly on tumor-suppression applications. However, because telomere length is a marker of cell division and, when critically short, induces senescence, it may also shed light on the relationship of early growth to later disease.

In this paper we argue that the emerging auxologic epidemiology of adult disease, spurred by the work of Barker and colleagues, might profitably consider the investigation of possible genetic underpinnings of both growth and senescence, shaped as they are by natural selection. Our aim is to review evidence for one such newly discovered chromosomal mechanism, telomere attrition, which may underlie the early origins of cardiovascular disease, and to discuss this mechanism in light of the evolution of senescence.

Evolutionary Theories of Aging

As we have discussed, variation in fetal and postnatal growth may influence the development of some of the common diseases of aging. In the continuing search for the mechanisms underlying the link between early growth and adult health, evolutionary theories of aging and senescence provide a valuable conceptual framework.

The idea that growth, maturation, and diseases of aging are intimately linked to each other has a long history in life history theory and evolutionary biology. A fundamental question with which early theorists struggled was how senescence and the decline in physiologic function of individuals could have evolved, because, all else being equal, longer-living individuals would be expected to have higher reproductive fitness (both direct and indirect) than would individuals with shorter life spans. Fisher (1930) was the first to discuss how senescence is a necessary outcome of the action of natural selection. By examining the theoretical relationship between the intrinsic rate of increase (the Malthusian parameter) and the survival function of a population, Fisher saw that the reproductive value of individuals at a given age could be identified. He stated that natural selection will shape the mortality structure of populations to minimize mortality when the reproductive cost to the population would be highest. As evidence, he showed that in organisms with a senescent life history, the mortality rate tends to closely follow the reproductive value. For example, in humans mortality reaches a nadir around age 10–15 years (the age of sexual maturity, and immediately before the initiation of reproduction) and tends to be higher at ages less than and greater than that age of peak reproductive value (Fisher 1930).

Peter Medawar (1946,1952) was heavily influenced by Fisher's ideas on the evolution of senescence (Charlesworth 2000). He reasoned that because post-reproductive individuals have relatively low reproductive value (i.e., they are essentially invisible to natural selection, at least directly), selection will be more effective in improving performance early in adult life than late in life. Therefore the strength of selection on a gene whose effects on survival or fecundity are confined to a given age or set of ages depends on the age or ages in question, such that the intensity of selection increases as the timing of gene action moves closer to the time of sexual maturation. Genetic mutations causing senescence and physiologic degeneration would be strongly selected against in nature if the mutations came into play before reproductive maturity, whereas those that are not expressed until later in life would not be selected against and could be maintained within the population. In this way, Medawar established how senescence is an evolutionary response to the diminishing effectiveness of selection with age [Medawar 1946,1952; reviewed by Charlesworth (2000)].

There are two major theories of how the decline in selective force with age may influence the process of senescence: antagonistic pleiotropy and mutation accumulation. In his landmark paper, Williams (1957) posited that, given the waning force of selection with age, some variant alleles positively selected during evolution on the basis of increasing early survival or improving reproductive efficiency may have harmful effects once the reproductive period has peaked. Termed *antagonistic pleiotropy*, Williams's theory states that a single gene or set of genes that increases reproductive fitness (e.g., through more rapid

growth and maturation early in life) may deleteriously affect the same or another trait later in life, perhaps leading to physiologic senescence (Williams 1957). Charlesworth (1994) demonstrated mathematically that a gene that has a positive effect on survival at an earlier age could be selected for even if it had a pleiotropic effect that produced decreased survival at a later age. From this inherent age-structured aspect of gene action, Charlesworth showed that genes that tend to produce senescence might become fixed in a population.

The second major theory stemming from the observation of a decreasing selective force with age is the mutation accumulation, or disposable soma, theory. Kirkwood (1977) and Kirkwood and Holliday (1975) suggested that the degenerative changes that are seen during senescence—including the two primary causes of death, vascular degeneration through atherosclerosis and decline in insulin sensitivity—are the outward manifestation of cell deaths caused by a failure to maintain integrity of DNA, RNA, and proteins and by the inability to replace defective cells with normal cells. Kirkwood and colleagues showed that there is an energy cost to the proofreading mechanisms needed to keep errors of transcription and translation at a low steady level. In unicellular organisms a low error level is essential for the continued existence of a clone of cells, but for species with a separation of soma and germ plasm (eukaryotic organisms), there is a selective advantage in *reducing* the accuracy of proofreading after some period of life. This is because the energy invested in repair mechanisms is lost if death is accidental, which it often is in the wild. Thus there is a limited and declining benefit of maintenance functions with age, against which their energetic costs must be weighed. If the reproductive advantages of imperfect repair are sufficiently great, they will outweigh the disadvantage of subsequent errors in protein structure and function and death. In this light, the disposable (aging) soma (body) is an evolutionarily stable consequence of natural selection working to optimize an organism's use of its energetic resources. As somatic mutations accumulate in the aged, increasing numbers of cells function abnormally or die because of the accumulation of random genetic inaccuracies and somatic damage, which contribute to disease (Kirkwood 1998; Kirkwood and Holliday 1986).

Indications of a trade-off between reproductive success and cardiovascular health can be seen in the epidemiologic literature. For example, as the number of children a woman has borne increases, the lower her HDL-cholesterol concentration tends to be (van Stiphout et al. 1987) and the more likely she is to have carotid atherosclerosis (Humphries et al. 2001). Some (but not all) studies have also shown inverse associations between parity and the risk of coronary heart disease (Kvale et al. 1994; Ness et al. 1993; Palmer et al. 1992) and stroke (Qureshi et al. 1997). Although these findings are in line with the predictions of the disposable soma theory, it is possible that the associations between parity and cardiovascular disease stem directly from hormonal and body composition changes inherent in pregnancy rather than from decreased investment in vascular tissue repair.

Both the antagonistic pleiotropy theory and the disposable soma theory stem from the fundamental observation that the force of natural selection weakens with advancing adult age. Because increased investment in DNA repair and proofreading means decreased investment in growth and reproduction, the disposable soma theory also provides a general explanation for the convergence of certain life history patterns (e.g., the observed correlation between rapid growth/early reproductive maturity and shorter life span across phyletic groups) (Stearns 1992). However, here we are most interested in finding a physiologic or genetic model that might explain, within individuals, how variation in fetal and infant growth in particular affects cardiovascular and other chronic disease risk later on. Although the thrust of work on the fetal origins of adult disease (Barker 1998) concerns environmental programming of cardiovascular senescence, there is evidence that antagonistic pleiotropy might in fact be at work. Genetic polymorphisms in the genes controlling insulinlike growth

factor (IGF) hormones are known, for example, to affect both fetal growth and later insulin sensitivity (Vaessen et al. 2002). Recent research on the biology of the chromosomal tips (telomeres) suggests another genetic mechanism that may account, at least in part, for the relationship between early growth and later disease (Aviv 1999; Jennings et al. 1999) and that may be an example of antagonistic pleiotropy at work.

The Telomere Hypothesis of Cellular Aging

Telomeres are noncoding functional DNA repeat sequences at the ends of chromosomes [5'-(TTAGGG)_n-3'] that are arranged in loop structures and function to stabilize the chromosome during mitosis, prevent aberrant recombination, and protect the chromosomes from end-degrading enzymes. After each cell division, telomeric base pairs are lost as a result of the inability of DNA polymerase to fully replicate chromosome ends (Olovnikov 1973). This “end replication problem” would have disastrous results if genetic information was contained in the chromosome tips. Thus the highly repetitive telomere sequences serve to protect chromosomes from loss of essential coding sequences. Harley (1991) said that the obligatory loss of telomeres with each cell division is a mitotic clock that marks the number of cell divisions that have taken place. The repetitive base-pair sequence and its telomeric location are highly conserved throughout evolution and appear to have originated early in the evolution of vertebrates (i.e., 400 million years ago) (Meyne et al. 1989), although the length of telomere DNA differs across species. Humans, for example, despite being among the most longlived species in nature, have relatively short telomeres, whereas the telomeres of laboratory rodents are very long despite their shorter life span (Campisi 2001). Why such species differences exist is still unknown.

In gametes, embryonic stem cells, and some tumor cells, telomere attrition with cellular replication does not occur because the enzyme telomerase remains active. Telomerase is a ribonucleic protein enzyme made up of an RNA template component and a catalytic protein component, called human telomerase reverse transcriptase (hTERT). Telomerase uses the internal RNA template to reverse transcribe telomeric DNA and extend telomeres after every cell division (Nakamura et al. 1997). It is in this way that germ-line cells and tumor cells remain immortal, capable of an unlimited number of cell replications (Niida et al. 2000). Activated telomerase therefore allows for the unrestricted cell proliferation characteristic of cancer.

In contrast, in differentiated somatic cells the hTERT component of telomerase is completely or partially inactivated (Kim et al. 1994; Niida et al. 2000). It is thought that telomeres in somatic cells eventually reach a critically short length, estimated at 4–6 kilobases (kb), from a maximum of approximately 20 kb, in one or more chromosomes, at which point further cell replication is impossible and the cell becomes senescent (the Hayflick limit) (Harley 1991; Harley et al. 1990). Experiments in which hTERT was forcibly expressed in cells that normally lack it showed that when telomerase activity was restored, telomere length was stabilized, and replicative capacity was regained (Bodnar et al. 1998; Weinrich et al. 1997). These landmark findings demonstrate that telomere shortening itself can signal cells to enter senescence and that telomerase is critical to cellular immortality. Once telomere length is critically shortened, DNA strand breaks occur, which could signal cell death by activating a number of different genes, including the tumor-suppressor gene p53 (Di Leonardo et al. 1994).

Thus the selective inactivation of telomerase in somatic cells but not in germ-line cells appears to be a mechanism that reduces the risk of uncontrolled cellular growth typical of cancer, and it simultaneously makes senescence inevitable by placing an upper bound on cellular life span (Bodnar et al. 1998; Weinstein and Ciszek 2002). Organisms exhibiting

this trait would likely benefit from an inherent barrier to hyperplasia, resulting in lower cancer death rates during the reproductive years and therefore increased fitness, but they would also be more likely to experience tissue dysfunction and death as a result of cellular senescence. The telomere hypothesis of cellular aging fits well with the prediction of Williams (1957) that aging mechanisms likely evolved through antagonistic pleiotropy. In this case, the early-life reproductive benefit of a cancer-limiting mechanism (telomerase inactivation) necessitates cellular senescence in later life.

Telomere Attrition and Cardiovascular Disease

The foregoing research established that the loss of telomeres is a necessary result of cell division (growth) and leads to replicative senescence in cells. Because cancer is a disease of uncontrolled cell proliferation, telomere research has focused strongly on applications to tumor suppression. Whether or not telomere shortening is also an important determinant of cardiovascular senescence must be established, however, if we are to argue that telomere shortening might underlie the epidemiologic evidence linking fetal and early postnatal growth to cardiovascular disease. As a starting point, a number of studies have shown that cardiovascular aging is associated with telomere shortening. Aviv and colleagues (Aviv 2001; Benetos et al. 2001; Jeanclos et al. 2000) have observed that pulse pressure (systolic pressure minus diastolic pressure) is a useful indicator of the biological age of the arterial system. Whereas systolic blood pressure increases with age in adults, diastolic blood pressure plateaus, which might be explained by a progressive stiffening of central elastic arteries. Pulse pressure and aortic stiffness are strongly influenced by age and sex, but once these factors were considered in multivariate statistical models, telomere length remained an independent predictor of pulse pressure (Jeanclos et al. 2000) and aortic stiffness (Benetos et al. 2001), with these effects being more evident in males than in females (Benetos et al. 2001).

Atherosclerosis, the formation of lipids and cell-rich lesions on the intimal or luminal surfaces of arteries leading to occlusion, thrombosis, and infarction, is the primary determinant of cardiovascular disease mortality in industrialized nations (Labarthe 1998). One of the most enduring and useful models of the development of atherosclerosis is the inflammatory or response-to-injury model (Moore 1981; Ross 1993). In this representation the vascular wall becomes injured over time by mechanical, hemodynamic, and immunologic factors stemming from hypertension, smoking, and hyperlipidemia, among other common stressors. In response, the vascular endothelium initiates an immunologic cascade, characterized by the adhesion of platelets and macrophages at the sites of damage (Ross 1993). What begins as a protective mechanism eventually becomes a pathologic condition, in that excess lipid becomes sequestered within the adhered monocytes, infiltrating the vascular wall and forming atherosclerotic plaques. As would be expected, given this model, telomere attrition is accelerated in arterial tissue exposed to high levels of shear and oxidative stress as cellular replication increases to repair the damaged tissues (Chang and Harley 1995; Okuda et al. 2000). The relationship between the severity of atherosclerotic lesions in the distal and proximal aorta and the telomere length of cells in these tissues was examined using autopsy samples in individuals of age 1 month to 80 years (Okuda et al. 2000). Raw correlations between telomere length and the severity of atherosclerosis were significant for the distal aorta ($r = -0.48$ for intimal tissue and $r = -0.40$ for medial tissue) but not for the proximal aorta. As expected, age was a strong predictor of the severity of atherosclerosis, and, in fact, after adjusting for age, the correlation was reduced ($r = -0.28$, $p = 0.06$). The sample sizes were small, and so it is unclear whether or not atherosclerosis directly enhances the rate of telomere attrition. Samani et al. (2001) reported that telomere length was significantly shorter (303 bp) in patients with coronary heart disease than in a control group. The number of patients with

coronary artery disease was small ($N = 10$) and included only 1 female, but restricting the analysis to males only strengthened the association (Samani et al. 2001).

Telomere attrition is associated with elevated blood homocysteine concentrations, a major cardiovascular disease risk factor known to accelerate atherosclerosis, and also with increased expression of the endothelial cell inflammatory markers ICAM-1 and PAI-1 (Xu et al. 2000). These latter findings suggest that, although the presence of atherosclerotic lesions may or may not accelerate telomere loss (Okuda et al. 2000), telomere length may be a biomarker for the earlier stages of endothelial cell senescence and the initiation of the atherosclerotic process, which is characterized by vascular inflammation. Jeanclos et al. (1998) found that the white blood cells of individuals with insulin-dependent diabetes mellitus exhibit reduced telomere length compared to a control group, providing a possible link to glucose tolerance as well.

Finally and perhaps most important, Cawthon (2002) recently found that mean telomere length, measured in blood DNA, can predict the 15-year risk of cardiovascular disease mortality. Specifically, Cawthon found a threefold higher risk of death from cardiovascular disease in both males and females among individuals with shorter telomeres (less than the median length) compared to individuals with longer telomeres (greater than the median length), adjusting for age at baseline. An eightfold higher risk of death from infectious disease was also found among males and females with shorter telomeres. As Cawthon noted, these results suggest that telomere length is causally related to increased risk of death but alternately could indicate that telomere length is a marker of disease or senescent processes that in turn increase the risk of death (Cawthon 2002).

Telomere Biology in Growth and Aging

Further research is clearly indicated, but the associations between telomere length and cardiovascular health suggest either that telomere shortening leads to cardiovascular senescence or that other proximate or distal determinants contribute to both. Even if it is found that cardiovascular senescence is not a direct outcome of telomere shortening, telomere length may still be a good biological marker of cardiovascular senescence. To disentangle these possibilities, we need to understand the biology of telomeres in greater detail. In this section we discuss what is currently known about telomere biology during growth and aging and outline the major physiologic factors that regulate telomere length in humans.

In a review of the rate of telomere length reduction, Takubo et al. (2002) reported that humans lose an average of 20–60 bp of telomere DNA per year of life (Allsopp et al. 1992; Harley et al. 1990), but this average rate obscures variation across and within different tissues. Cross-sectional estimates of the rate of telomere shortening, derived from linear regression of telomere length on the age of the individual, ranged from slow rates of change (e.g., 9 bp/yr in renal medulla, 15 bp/yr in fibroblasts, and 20 bp/yr in epidermal cells) to rapid rates of change (e.g., 120 bp/yr in hepatic tissue and 47–147 bp/yr in vascular intimal tissue) (Takubo et al. 2002).

There also are possibly important fluctuations in telomere attrition at different points in growth, development, and aging. Recent findings show that organspecific rates of telomere length change are evident during the fetal period. Ulaner et al. (2002) found similar mean telomere lengths in fetal liver, heart, and kidney at 8 weeks of gestation (approximately 15–17 kb). Thereafter, telomere length was stable in fetal liver but declined rapidly to 9 kb in fetal heart and 12 kb in fetal kidney (Ulaner et al. 2002). The onset of telomeric attrition in these fetal tissues was found to closely follow the repression of hTERT mRNA, which occurs at 11 weeks in the heart and 15 weeks in the kidney but does not occur at all in the

liver (Ulaner et al. 2002). Conversely, the *postnatal* rate of telomere loss appears to be relatively high in the liver (60 bp/yr) and low in the heart (nonsignificant decline) (Takubo et al. 2002). This contradiction is an indication that qualitative differences in prenatal and postnatal telomere biology exist.

In a cross-sectional study Frenck et al. (1998) found that, after a precipitous decline in mean telomere length during early childhood (ages 0 to 5 years), mean telomere length in leukocytes stabilizes until approximately age 20, after which a slow rate of attrition occurs during adulthood. Most research has, indeed, found a similar monotonic decline in telomere length of different cell types in the adult period (age 30–100 years) (e.g., Allsopp et al. 1992; Friedrich et al. 2000). Thus the fetal period is characterized by rapid organ-specific decline in telomere length following the selective inactivation of telomerase activity in different organs and a slower but still relatively rapid loss of telomeres during early childhood (up to age 5 years). Thereafter, a stable period in telomere length appears to exist from mid-childhood until mid-adulthood, despite this being a period of rapid tissue growth. However, the study of Frenck et al. (1998), upon which this observation is largely based, did not have DNA samples from individuals between the ages of 5 and 20 years, thus leaving open the question of adolescent fluctuations in telomere loss. Finally, middle to late adulthood is characterized by a fairly slow linear decline in mean telomere length. In addition to variation across age and tissue type, different regions of the same tissue may show variation in telomere loss. Decline in telomere length with age was discernible in the distal abdominal media ($r = -0.5$) but not in the proximal abdominal media (Okuda et al. 2000).

It was initially assumed that higher rates of telomeric loss would be found in tissues with higher rates of cell turnover, as would be expected if telomere length was related solely to the pace of cell replication, but this assumption has not been supported. Gastrointestinal mucosal epithelia, a rapidly renewing cell type, has a slower rate of telomere attrition than liver or kidney cells, despite the slower rate of renewal in these tissues (Takubo et al. 2002). Relatedly, strong correlations are found within individuals between the rate of telomeric loss in various tissues in the body, despite their widely differing replicative histories. These intra-individual correlations are found between peripheral blood monocytes and fibroblasts (R. von Zglinicki et al. 2000) and between leukocytes, skin cells, and synovial tissue (Friedrich et al. 2000). Takubo et al. (2002) and others have observed that even within a single tissue type from an individual, there exists great variation in telomere length, as evidenced by wide smears of telomeric DNA in Southern blot analyses, which may be attributable to differences in telomere length across different cell types and chromosomes within a given tissue.

An emerging consensus points to the great interindividual variability in telomere length and the high intra-individual consistency in the rate of telomere attrition from widely differing tissues as evidence that telomere length is a marker of the general biological age of the individual (even given the intra-individual variation among cells and chromosomes) rather than a reliable mitotic clock in individual tissues. Longitudinal data tracking telomere change during growth and aging and its correspondence with changes in endothelial damage and other precursors of atherosclerosis will clarify our view of cellular aging as it relates to the development of cardiovascular disease.

Factors Regulating Telomere Length

Given the variability in telomere length and the rate of telomere shortening between individuals, the search is on for regulatory factors that control telomerase function and protect telomeres. Antioxidant capacity is one such factor under investigation. One of the

fundamental mechanisms of aging is the accumulation of oxidative damage (T. von Zglinicki 2000). All aerobic organisms have evolved defenses against reactive oxygen species or free radicals produced as the byproduct of oxidative metabolism within cells, and, in general, long-lived species have better antioxidant defenses than short-lived species (Kirkwood 1998). Even so, long-lived species such as humans accumulate aberrant proteins, defective mitochondria, lipid peroxidation, and damaged DNA with age as a result of insufficient antioxidant capacity needed to quench the action of free radicals. Oxidative stress appears to be a major regulatory factor affecting the loss of telomeres. The work of T. von Zglinicki and colleagues (Lorenz et al. 2001; Petersen et al. 1998; Saretzki et al. 1999; Serra et al. 2000; Sitte et al. 1998; T. von Zglinicki 1995, 2000; T. von Zglinicki et al. 2000) has established that oxygen free radicals are a major cause of telomere shortening in vitro and that reduction in oxidative stress reduces the rate of telomere shortening. Saretzki and von Zglinicki (2002) have shown that the rate of telomere shortening in different cell types correlates with their intrinsic antioxidant capacity, suggesting that telomere length reflects the cumulative history of oxidative damage a cell line has experienced and perhaps also marks the ability of the individual to cope with oxidative stress.

Telomere lengths are greater in women than in men (Benetos et al. 2001; Jeanclos et al. 2000), as might be predicted given the greater longevity of women. Recently, it has been shown that this sex difference might be directly due to the effects of estrogen. Estrogen activates the telomere reverse transcriptase hTERT through direct and indirect effects on the hTERT promoter gene (Kyo et al. 1999). This effect was documented in estrogen-receptor positive breast cancer cells, showing how estrogen-sensitive cancers might be initiated, but it is possible that other estrogen-responsive tissue types (e.g., the arterial wall) might also have the potential for telomerase activation.

The effect of estrogen on telomerase activity is also evident in the rise and fall of telomerase activity across the menstrual cycle. Endometrial telomerase activity is undetectable during menstruation but increases during the follicular phase, peaks immediately before ovulation, and then falls during the luteal phase (Kyo et al. 1999; Tanaka et al. 1998). Because telomerase activity appears to be hormonally induced in subsets of somatic cells, greater female longevity may be due in part to a slower rate of telomere attrition in women secondary to estrogen exposure. However, it should be noted that estrogen has other, more firmly established protective effects on the cardiovascular system (Forte 1997; Rubanyi and Kauffman 1998) that are likely to be independent of the telomere mechanism.

Aviv (2001,2002) has hypothesized that additional steroid hormones involved in cell growth may also affect telomerase activity. This possibility affords yet another avenue for research focused on the hormonal orchestration of early growth, cardiovascular disease risk, and biological aging.

Although oxidative stress/antioxidant capacity and steroid/growth hormone concentrations are probable regulators of telomere length, genetic factors are likely to underlie these proximate determinants, because high heritabilities have been found for telomere length. Slagboom et al. (1994) estimated that the additive effect of genes accounted for 78% of the variation in lymphocyte telomere length in a study of twins. This finding was confirmed by Jeanclos et al. (2000), who used a variance components approach to estimate heritability of the telomere length of white blood cells in twins. In that study, 84% of the residual variability was explained by genetic factors, after accounting for the contributions of sex, body mass index, pulse pressure, and age (Jeanclos et al. 2000).

The large degree of interindividual variation in telomere length, the strong correlations between telomere lengths of different tissues within individuals, and the apparently high

familiarity of telomere length in blood cells all suggest that telomere length at birth, its rate of shortening, or both are genetically determined. To further understand the rate of shortening, future research could be reasonably focused on genes that regulate antioxidant capacity and steroid and growth hormone function (Aviv 2001,2002). The high genetic contribution to telomere length and its high degree of interindividual variation furthermore reveals that natural selection's necessary substrate—genetic variation—exists for the telomere–telomerase control system. In Figure 1, we show a conceptual model that summarizes the links between genes, growth, telomeres, and cardiovascular disease that have been documented thus far in the literature. If the expression of genes that control both growth and telomere length is found to vary in an age-dependent fashion, this would constitute an example of antagonistic pleiotropy operating to induce cardiovascular senescence.

Telomere Attrition and the Early Origins of Cardiovascular Disease

It has been known for approximately 60 years that postnatal growth restriction enhances longevity (McCay et al. 1939). Berg and Simms (1960) found that only half of rats fed regular food ad libitum survived to 800 days, whereas over 80% of rats that were severely calorie restricted (calories reduced by 33–46%) did so. Accompanying the effects on life span, food restriction retards age-related disease processes, such as loss of muscle and bone mass, loss of immune function, and collagen changes (Fernandes et al. 1978; Masoro et al. 1989; Yu et al. 1982). The telomere hypothesis of cellular aging provides explanations for these observations. If food restriction slows DNA synthesis and the rate of cell division, telomere loss could be slowed directly. Also, oxidative stress secondary to the metabolism of dietary fuels might be slowed, thereby retarding free radical damage and telomere attrition (Jennings et al. 2000; T. von Zglinicki 2000).

In a series of notable recent experiments, fetal growth retardation followed by rapid postnatal catch-up growth resulted in significant telomere attrition in the kidneys of rodents (Aviv 2001; Jennings et al. 1999). In one experiment, pregnant and lactating rats were fed a diet reduced in protein content to approximately half the normal intake for scheduled 3-week periods. The offspring were then placed on a normal diet and fed ad libitum. The prenatal protein-restricted rats experienced complete catch-up growth, but the postnatal protein-restricted rats remained permanently growth stunted compared to a control group. Only 25% of prenatal protein-restricted rats survived to 1 year of age, compared to 70% of control group rats and 87% of the postnatal protein-restricted rats. Telomere lengths from liver, kidney, and brain cells of the offspring were measured at various points in postnatal life and the lengths were compared between the three groups. Telomere length tracked the growth rate of the animals, such that there was a period of rapid loss during early life, presumably as a consequence of rapid growth during this time. Telomere length then remained fairly stable between 3 and 8 months of age, followed finally by a pronounced phase of shortening toward the end of the life span. Most important, there were significant differences in renal telomere length between the prenatal and the postnatal protein-restricted groups. The group of rats that experienced prenatal growth restriction had shorter life spans and shorter kidney telomeres compared to control animals (Jennings et al. 1999), whereas rats that experienced growth retardation in postnatal life had significantly longer kidney telomeres and increased longevity compared to control group rats. These benefits in the postnatal growth-restricted group corroborate previous research showing the survival advantage of hypocaloric diets. The disadvantages of renal telomere attrition and reduced life span in the group that experienced prenatal growth restriction, on the other hand, could explain the epidemiologic evidence linking both lower birth weight and rapid postnatal growth to later hypertension, insulin insensitivity, and coronary heart disease.

The study design used by Jennings et al. (1999) did not allow for the independent effects of prenatal growth retardation and postnatal catch-up growth to be addressed (i.e., all prenatal growth-restricted rat offspring were placed with an ad libitum-fed dam for lactation). It is therefore difficult to ascertain whether prenatal and postnatal growth restriction truly have opposite effects on telomere length, or whether catch-up growth, which was consistently observed in the prenatally restricted rats, was the operative characteristic driving the reduction in telomere length. Nonetheless, this study suggests that telomere shortening may underlie the observed associations between fetal growth retardation, catch-up growth, and hypertension in humans (Aviv 1999). Specifically, it demonstrates how growth restriction in utero, followed by catch-up growth, might prematurely age the individual in terms of reducing the replicative capacity of certain subsets of cells in the kidney. To date, these observations have been neither replicated nor refuted by other studies, either in rodents or in humans. This, the most direct evidence yet that telomere shortening is involved in the relationship between growth and cardiovascular disease, awaits corroboration and further study. Physiologic mechanisms by which fetal growth retardation accelerates telomere loss (despite the presumed slower rate of cellular replication) make up one major gap in existing knowledge.

Conclusions

Existing studies support the notion that telomere length is a genetically and environmentally controlled marker of the biological age of the cardiovascular system. Because of the known loss of telomeres in cell replication and at particular points in growth and development, telomere length might also be a cumulative reflection of growth rate across the life span. However, telomere length has not been found to be a reliable reflection of the replicative history of different tissues, which clouds the relationship between growth rate and telomere length. It is possible that residual or hormonally induced telomerase activity in somatic cells might repair telomeres in rapidly dividing cell types, at least at particular points in development. Nevertheless, the search is on for environmental and genetic regulators of telomere length and telomerase function in humans. Given that most of the published studies are based on in vitro experiments or on tissue specimens collected at a single age, individual variation in the rate of telomere attrition and how this might relate to growth rate and the rate of decline in vascular endothelial and metabolic function in individuals is not yet known. Thus the intriguing hypothesis forwarded by Aviv and colleagues (Aviv 1999, 2001, 2002; Benetos et al. 2001; Jennings et al. 1999, 2000), that fetal and postnatal growth variation are linked to hypertension by means of their effects on cellular senescence, awaits confirmation and extension to humans. That vascular inflammation, oxidative stress, and coronary artery disease are related to telomere length suggests that this mechanism might hold not only for hypertension but also for atherosclerosis. We argue that there exists a critical foundation for a new focus in chronic disease epidemiology that tackles the basic genetic mechanisms linking early growth to later cardiovascular disease. The study of telomere attrition may ultimately shed light on the evolution of senescence in the human species, with its markedly long life span and unique pattern of fetal, infant, and adolescent growth.

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Figure 1.
Model summarizing links between growth rate and cardiovascular senescence through telomere attrition.