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Growth, telomere dynamics and successful and unsuccessful human aging

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Abstract

This paper links mass trajectories with telomere dynamics to construct theoretical models of successful and unsuccessful aging in human beings. It couples parameters of telomere length in somatic cells, as expressed by the terminal restriction fragment (TRF), at birth and the rate of telomere attrition thereafter with nonlinear models of somatic growth to predict the probability of surviving disease free, based on the assumption that telomere length in replicating somatic cells is a surrogate indicator of aging determinants in humans. The models capture aspects of individual variation in successful and unsuccessful aging and the long-term consequences of rapid growth early in life.

Keywords: Telomeres; Aging; Growth; Somatic cells; Replication

1. Introduction

In modern humans, aging portends an escalating risk of developing age-related disorders, including cardiovascular disease, diabetes mellitus, cancer, dementia, and a host of degenerative diseases which ultimately lead to death. Accordingly, aging has been frequently defined in terms of the increased probability of death, i.e. the risk of dying as a function of age (Partridge and Mangel, 1999). The endpoint of aging is, no doubt, death, but defining this complex biological process by its ultimate outcome leaves a considerable void with respect to a central question in gerontology. That question—how to explain and predict disorders of aging in the context of the biological meaning of aging—has considerable clinical relevance. Such disorders arise from progressive dysfunctions in metabolism, particularly impaired tissue repair capacity, leading to degeneration of tissues and organs—a phenomenon expressed by the cumulative compromise that ultimately results in death.

There is, however, considerable variation in the rate of progression of aging in humans. Perhaps one way to explore the underlying reasons for this variation is to distinguish unsuccessful from successful aging. In unsuccessful aging, age-related disorders appear to proceed faster or start earlier than in successful aging. Consequently, the clinical manifestations of these disorders are more severe and expressed at a younger (chronological) age, causing premature disability and death. Unsuccessful aging may hence be viewed as a process of early onset aging or accelerated aging and it could occur in isolation in one organ system, progress independently in a number of organ systems, or proceed uniformly in the body as a whole.

Given the enormous complexity of organisms, a simple biological model of aging is obviously inadequate for all purposes. Nevertheless, such a model may guide the design of both empirical and experimental work, facilitating the distinction between unsuccessful and successful aging. In this paper, we combine clinical observations and theoretical biology to construct a

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mathematical model that links recent advances in modeling growth (West et al., 2001) with insight gained into telomere biology (Blackburn, 2000; Klapper et al., 2001; de Lange, 2002) and its potential link with the biology of human aging (Aviv, 2002). The model, we suggest, points to new ways of looking at and searching for the biological mechanisms of aging.

1.1. Telomeres, somatic cell replication and replicative senescence in vitro

Human telomeres consist of many kilobases of TTAGGG tandem repeats and telomeric binding proteins, which together cap the ends of chromosomes and protect them from degradation and end-to-end fusion (Blackburn, 2000; Klapper et al., 2001; Chan and Blackburn, 2002; de Lange, 2002; Kim et al., 2002). Because of the end replication problem (Watson, 1972; Olovnikov, 1973), telomeres undergo erosion with each cycle of replication of cultured somatic cells, until the telomere length (probably telomere length in those chromosomes with the shortest telomeres) becomes sufficiently shortened. At this stage, a poorly understood signal triggers cessation of replication, i.e. replicative senescence (Wright and Shay, 2001). Thus, telomere length is not only a record of replicative history but also an index of replicative potential of cultured somatic cells from humans. Telomere attrition may also affect the silencing of gene expression in the gene-rich sub-telomeric regions, thereby modifying cell biology before the onset of replicative senescence (Baur et al., 2001). Recent data suggest that protecting the chromosomes from end-fusion events may not be strictly related to telomere length but to the configuration of telomeric DNA in relation to telomeric binding proteins (Blackburn, 2000; Chan and Blackburn, 2002; de Lange, 2002; Karlseder et al., 2002). Critically shortened telomeres evidently trigger replicative senescence because they lose the protective shield of their telomere binding proteins.

Telomere attrition in cultured somatic cells can be influenced by at least six processes: (a) the initial telomere length in the primary (progenitor) cells; (b) the rate of replication; (c) the length of the G-rich 3′ single stranded telomere overhangs (SSOs) (Wright et al., 1997; Huffman et al., 2000), which determines how much DNA is lost per division; (d) the regulation of telomerase, (Bodnar et al., 1998; Morales et al., 1999; Shay et al., 2001) which is expressed in many stem cells and which slows but does not prevent telomere shortening; (e) the pattern of cell division (the fraction of self-renewal vs. generation of transient amplifying cells); and (f) the contribution of other factors such as oxidative damage which can contribute to telomere shortening in a fashion not strictly related to the number of divisions (von Zglinicki et al., 2000; Serra et al., 2003). In this manuscript we will explore the potential influence of the first three factors. In addition, a number of non-telomerase telomere binding proteins, including TRF2 (in telomerase-negative cells), and TRF1, TIN2 and hRAP1 (in telomerase-positive cells) are involved in stabilizing telomere structure and regulating telomere erosion (van Steensel and de Lange, 1997; de Lange, 2002; Kim et al., 2002). Overall, these experimental observations are in line with the idea that telomeres are a mitotic clock in cultured somatic cells from humans and that telomere length reflects, in part, the replicative history of these cells (Harley et al., 1992).

1.2. Telomere dynamics in vivo

The following features mark human telomere biology in vivo. During intra-uterine life, telomere length is stable and synchronized (i.e. it is approximately the same) in different organs and tissues, evidently because of robust telomerase activity during different phases of intra-uterine growth (Wright et al., 1996; Youngren et al., 1998) telomere length is inversely related to the donor age in tissues that undergo proliferation (Allsopp et al., 1992; Slagboom et al., 1994; Kitada et al., 1995; Jeanclos et al., 1998, 2000; Okuda et al., 2000; Aviv et al., 2001; Benetos et al., 2001); telomere length is highly heritable (Slagboom et al., 1994; Jeanclos et al., 2000), longer in women than men (Jeanclos et al., 2000; Benetos et al., 2001) and is highly variable among humans; this variability is observed at birth and thereafter (Slagboom et al., 1994; Okuda et al., 2002). Although cells from highly proliferative somatic tissues may express some telomerase activity, this activity is insufficient to prevent age-dependent telomere attrition. During extra-uterine life, much of the age-dependent telomere attrition probably reflects cell replication in the soma. Two lines of evidence further support this idea: post-mitotic, poorly proliferative tissues such as skeletal muscle show little or no telomere erosion with age (Decary et al., 1997). Despite considerable proliferation, male germlines, which also express high telomerase activity, show no age-dependent telomere erosion (Allsopp et al., 1992; Wright et al., 1996).

1.3. Telomeres, chronological age and biological age

Telomere dynamics may serve as an index of biological age if: (a) the cumulative number of replications of somatic cells; (b) the rate of somatic cell replication; (c) other factors such as the cumulative oxidative stress; or (d) any combination of these variables register growth and aging of humans. Biological age is different from chronological age—a fixed quantity that is based on the calendar—in that biological age reflects inter-individual variation in rates and expressions of growth and aging. If telomere dynamics simply tracked chronological age,

telomeres would provide little information beyond that of chronological age about the biology of human aging. Deciphering the reasons for variation in telomere dynamics among humans may thus provide a better understanding of successful and unsuccessful aging.

White blood cells (WBCs) are proliferative cells and are readily available from humans. These cells have been used to explore whether telomere dynamics can provide information, additional to chronological age, about susceptibility to disorders of aging.

The primary focus has been on the relationship between telomere length in WBCs and indices of cardiovascular aging. One of these indices is pulse pressure, which is a reliable indicator of the biological aging of central arteries such as the aorta. Elevated pulse pressure entails a heightened risk for cardiovascular diseases, particularly, atherosclerotic coronary heart disease (Franklin et al., 1999, 2001; Lakatta and Levy, 2003). Telomere length, as expressed in WBCs, is inversely correlated with pulse pressure, so that even after age adjustment, individuals with a shorter telomere length are likely to show a higher pulse pressure than their peers (Jeanclos et al., 2000; Benetos et al., 2001). This may explain why individuals with shorter telomere length than their age-matched peers may have an increased risk for atherosclerosis (Samani et al., 2001). Short, age adjusted telomere lengths in WBCs or subsets of WBCs have been also observed in individuals diagnosed with different forms of dementia (von Zglinicki et al., 2000; Panossian et al., 2003). It follows that a relatively short telomere length in WBCs may denote unsuccessful aging and an increased risk for premature death from age-related disorders (Cawthon et al., 2003). Given that telomere dynamics may provide clues regarding the biology of aging, a model linking telomere dynamics with successful versus unsuccessful human aging is in order.

1.4. A modeling framework and its predictions

The extreme boundaries of the continuum that comprises lifespan, i.e. growth and aging, are clearly defined by conception (the beginning) and death (the end). Other than these boundaries, there are no clear-cut demarcations between phases of the continuum. Maturation is evidently a phase bridging development with aging. In general, however, there are no distinct set-points that can be used to clearly and precisely mark transitions from growth to maturation and from maturation to aging (i.e. maturation and aging are not knife-edge processes but are continuous). Consequently, it is impossible to define accurately, in temporal terms, phases within the continuum. Instead, one might view growth and aging as dynamic, but partially overlapping processes, from both the temporal and functional perspectives.

West et al. (2001) have shown that a wide variety of organisms have mass trajectories that can be described by the non-linear differential equation:

$$\frac{dw}{dt} = aw^{3/4} - bw \quad (1)$$

where w(t) is mass at time t (or age, since we treat them interchangeably here because we are not considering the demography of overlapping generations) and a and b are anabolism (tissue building) and catabolism (tissue breakdown). The key feature of equation 1 (Fig. 1) is progression from a non-steady state early in life to a steady state later in life. One should regard a and b as species-specific parameters and we treat them as constant. Although they may slowly vary over the course of the life of an organism, the choice of constant a and b is a useful first approximation and allows us to recognize that organisms achieve at least a pseudo-steady state for much of their lives. Furthermore, West et al. (2001) show excellent fit between this growth model, with constant parameters, and mass trajectories for a wide variety of organisms.This model captures many aspects of somatic growth, but disregards some of the features that occur at finer time scales (Hermanussen et al., 1996, 1998a,b). The transformation $w(t) = H(t)^4$ converts equation 1 to a linear equation for H(t). After this equation is solved for H(t), we convert back to w(t) and then treat w(t) on an annual time scale.

In modern humans, body mass tends to decline in old age due to atropy of post-mitotic tissues such as skeletal muscle. Even the human brain manifests age-related atropy associated with loss of neurons. However, there is no information regarding the extent of loss, if any, of proliferative tissue mass. We, therefore, assume that replicative cell mass is relatively stable during human maturation and aging.

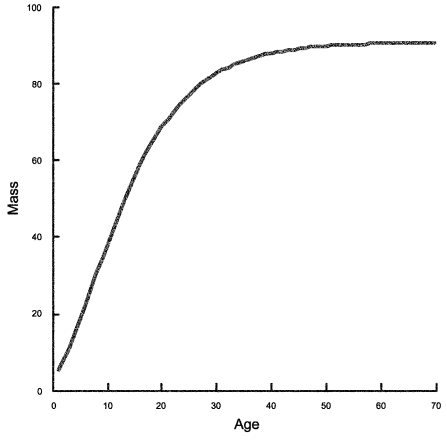

Fig. 1. Dynamics of mass predicted by Eq. (1), for an initial mass of 3.4 kg and an asymptotic mass of $w_{inf} = 90.9$ kg when the parameter $a = 1.31$. The parameter b in Eq. (1) is determined by the relationship: $b = \frac{a}{w_{inf}^{0.25}}$.

In order to link mass trajectories with telomere dynamics, we incorporate into the model the concept that telomere attrition reflects the replicative history of somatic cells. West et al. (2001) show that the parameters a and b can be interpreted as:

$$a = \frac{B_0 m_c}{E_c} \quad \text{and} \quad b = \frac{B_0}{E_c} \tag{2}$$

where B_0 is a taxon dependent constant; m_c, the mass of a single cell and its associated extracellular matrix; E_c, the energy required to make a single cell and B_c is the metabolic rate of a single cell. At any age, $w(t) = m_c N_c$, where w is the mass and $N_c(t)$ is the number of cells comprising the organism. Consequently, if one assumes that in replicating tissues of the soma hypertrophy (growth related to an increase in cell mass) is small relative to hyperplasia (growth related to an increase in cell number), changes in mass of these tissues are reflected linearly in changes in the number of cells. In addition, sustaining tissue growth through hypertrophy still requires an increase in vascular supply and perhaps in nutrient absorptive capacity via the gastrointestinal tract. One, hence, anticipates that cells in these and related tissues would have an increase proliferative rate to accommodate growth and turnover. Similarly, at steady state (i.e. near asymptotic size), maintenance (housekeeping) of the soma requires the turnover of a fraction of cells.

To describe telomere dynamics in vivo, let L(t) in equation 3 denote the average telomeric length (as expressed by the mean length of the terminal restriction fragments) at age t, and assume that telomere dynamics is given by the discrete time (annual) dynamics:

$$L(t+1) = L(t) - s\left[\Phi_g \frac{w(t+1) - w(t)}{w(t)} + \Phi_m w(t)\right] \tag{3}$$

where s is an annualized measure of telomere repeats lost per cell division (TRLPD), and Φ_g and Φ_m, respectively, relate to TRLPD as a result of cellular proliferation that promotes growth and turnover associated with housekeeping. We consider Φ_g and Φ_m to be species-specific constants, much as is B_0 in the growth model.

Recent studies found that the rate of TRLPD is proportional to the length of the SSOs (Wright et al., 1997; Huffman et al., 2000). It is possible, therefore, that in vivo variation in age-dependent telomere erosion may largely relate to the length of the SSOs. For this reason, we incorporated into our model the length of the SSOs, based on available data. For purposes of computation, the length of the SSO is assumed to range from 0.075 to 0.175 kb, with a mean of 0.125 kb and a coefficient of variation of 20%. The rate of loss of telomeres at asymptotic size is assumed to be 0.03 kb/year (Allsopp et al., 1992; Slagboom et al., 1994; Kitada et al., 1995; Jeanclos et al., 1998, 2000; Okuda et al., 2000; Aviv et al., 2001; Benetos et al., 2001; Okuda et al., 2002) when SSO length = 0.125 kb. However, as expressed in WBCs, early in life the rate of loss of telomeres is much higher (Frenck et al., 1998; Rufer et al., 1999; Zeichner et al., 1999) and the early life loss rate allows us to determine Φ_g. We note in this regard that the etiology of rapid telomere attrition in early life is unclear. It has been attributed to an increased cellular turnover, but in theory it can relate to a host of factors among them a longer SSO length. In our model, we assumed that the SSO length is constant throughout life.

We have thus specified the dynamics of proliferative somatic growth and of telomeric attrition. We now assume that telomeric length is a biomarker for the probability of disease, regardless of whether in itself telomere dynamics is a determinant in the biology of aging or a surrogate indicator of other aging determinants. The relationship between the annual probability of remaining disease free and telomere length L(t) at the start of a year is currently unknown (indeed, one role of theory is to point out what needs to be measured). Consequently, we modeled it as $\exp(-0.8(L(t)-3))$, for the following reasons. First, the exponential distribution is the simplest of all survival distributions; hence it is a parsimonious choice. Second, with the exponential model, the probability of remaining disease free depends only upon current telomere length, and not the dynamics of age-dependent telomere attrition, thus making it a practical choice for empirical studies. The parameters 0.8 and 3 were chosen by coupling the model for the probability of disease development with the mass and telomere length dynamics for an individual with mean initial telomere length and mean loss of telomere repeats per cell division to give a probability of about 50% of reaching age 70 disease free.

We applied this model to a population of 500 individuals, assuming that all individuals have the same growth trajectory, but differed in initial telomere length (which we assumed was normally distributed with mean 11 kb (33) and standard deviation 1.2 kb). We were thus able to generate a survival trajectory for the population, while at the same time following the histories of individuals.

To illustrate the latter point, we randomly picked five individuals from the sample of 500. In Table 1, we present the TRLPD(SS0), initial telomere length and the probability that each individual survives to age 45 free of age-related disease. Note that both initial telomere length and TRLPD determine this probability. We can then pose the question: given that an individual has reached age 45 without clinical findings of cardiovascular disease, diabetes, cancer, etc., what is the predicted probability of surviving to future ages free of age-related diseases (Fig. 2). The results in this figure are analogous to the emperical ones, in which individuals were

Table 1
Telomere repeat loss per cell division (TRLPD), initial telomere length and probability that five randomly picked individuals survive disease free to age 45

Individual number	SS0 (kb)	Initial telomere length (kb)	Probability of survival disease free to age 45
270	0.145	11.56	0.79
39	0.125	10.48	0.64
420	0.134	9.97	0.47
268	0.155	8.39	0.03
257	0.134	10.12	0.51

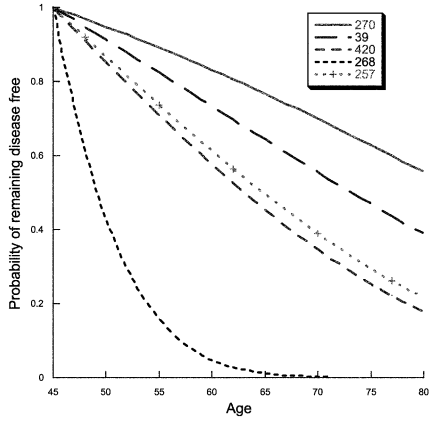

Fig. 2. The probability of remaining disease free for each of the simulated individuals in Table 1, given that they are disease free at age 45. This set of model predictions is in analogy to the empirical work (Cawthon et al., 2003) that has related survival after age 60 to longer or shorter telomeres.

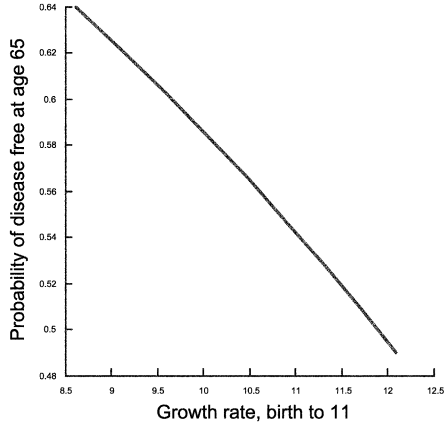

Fig. 3. The relationship between growth rate between birth and age 11, and the probability of remaining disease free, as predicted by the model.

separated into groups that had longer or shorter telomeres (Cawthon et al., 2003). This model allows us to be more precise about such relationships.

We also conducted a computer experiment to simulate accelerated growth during early development. To do this, we held birth mass constant, varied asymptotic size, and assumed that all individuals had the same initial telomere length and loss of telomere repeats per cell division (since telomere length appears unchanged in utero (Youngren et al., 1998)). In Fig. 3, we show the relationship between growth rate to age 11 (defined as $[w(11)-w(0)]/w(0)]$) and the probability of reaching age 65 disease free.

Figs. 2 and 3 suggest a variety of scenarios that may define unsuccessful and successful aging from the perspective of replicating somatic cells, organs, tissues, or the organism as a whole. One obvious scenario is that unsuccessful aging may be the result of deviations from the growth trajectory that lead to accelerated growth and that the ultimate body size is a determinant in successful versus unsuccessful aging. It is, hence, noteworthy that a body of epidemiological data suggests that height inversely correlated with longevity (Samaras et al., 2003). Furthermore, the results suggest additional scenarios linking telomere biology to aging. They include: an increase in proliferative, non-malignant growth of specific somatic tissues, an increase in cellular turnover associated with housekeeping, an increase in tissue breakdown that generates a cellular response resulting in enhanced cell replication, and different combinations of these possibilities. Of relevence to people in industrialized societies, particularly the USA, is an increase in body mass due to obesity. Gain in adiposity (fat mass) during adult life is attained primarily through hypertrophy of fat cells. However, as indicated earlier regarding hypertrophic growth, the increase in fat mass may be accompanied by considerable angiogenesis to accommodate the metabolic needs of the growing fat tissue (Samad et al., 1998; Li et al., 2002; Rupnick et al., 2002). This entails proliferative growth of vascular cells and hence telomeric erosion. The vascular endothelium of newly formed fat mass may hence exhibit more aged features, which might contribute, for instance, to insulin resistance, associated with obesity.

If telomere length itself is not only a biomarker but also a determinant in aging, we predict that short telomeres length at birth and a greater TRLPD will be ultimately linked with unsuccessful aging. If TRLPD is correlated with the SSO length, the SSO length may be a factor in unsuccessful aging. To date, data about

variation in the length of the SSOs have been observed only with respect to cell types (Wright et al., 1997; Huffman et al., 2000), so that the SSO length would only be relevant to aging of different tissues within the individual. However, the model may also apply to inter-individual variation in successful and unsuccessful aging if it turns out that consistent variation in the SSO length exists among individuals.

Inter-species comparisons in telomere length have been used in support of the tenet that telomere dynamics is not a determinant of mammalian aging. Telomere length of some mice species is similar to that of humans yet humans have by far a longer life span than mice (Wright and Shay, 2000). In addition, telomere length may differ considerably among mice species that have a similar life span. However, a strong case for or against the role of telomere dynamics in aging may not be derived from inter-species comparisons. Phenotypic expression of genes or suites of genes largely depends on their genetic and environmental milieu. Telomeres may have little or no function in the aging of the organisms in which other determinants bring about demise long before telomere length may become a factor in aging. Considering multi-factorial and complex nature of aging, conclusions about aging determinants based on inter-species comparisons without regard to genetic background are clearly misplaced. If mice do not exhibit replicative aging, there is no reason why the length of their telomeres should correlate with their life span. For instance, compared with humans, small mammals with a short life span produce considerably larger amounts of reactive oxidative species (ROS) and have less ability to detoxify ROS (Barja, 1998; Beckman and Ames, 1998; Finkel and Holbrook, 2000). If ROS figure in aging, mice are likely to succumb to the cumulative effect of oxidative stress long before their telomere length becomes a factor in aging. In addition, when telomere length is critically shortened within the life span of a mouse, as shown in the telomerase knockout mouse, it appears that telomeres do have a role in the expression of some aging phenotypes (Lee et al., 1998; Rudolph et al., 1999; Wong et al., 2003). It is noteworthy, nonetheless, that the telomerase knockout mouse is in fact a sick mouse, and it may be a good model for diseases such as dyskeratosis congenita (Vulliamy et al., 2001). In this disease, critically short telomeres become a limiting factor in tissues such as the hematopoeitic and gastrointestinal systems, in which telomerase may attenuate telomere shortening. The main question is whether in humans telomeres can become short enough to alter gene expression in subtelomeric regions or loose their protective shield of telomere binding proteins within the individual's life span, so that telomere dynamics play an active role in aging.

1.5. Telomere dynamics and the genetics of aging

The trajectories predicted by our model may have ramifications about the effect of evolution and, hence, genes in the biology of human aging. Both growth and aging are driven by the temporal activation/silencing of hierarchies of genes. These genes can be broadly categorized as genes engaged in driving growth towards maturation and asymptotic somatic size, genes that pace aging by retarding or accelerating tissue breakdown, and genes involved in both processes. The common denominator for genes that may be responsible for unsuccessful aging would, therefore, be their ability to augment proliferation of somatic cells to attain not only the individual's ultimate body mass but also promote rapid growth and cellular turnover rates. Telomere dynamics would register all of these processes. The ability to monitor proliferative somatic growth of different tissues in vivo through telomere dynamics may be helpful in testing hypotheses that attempt to explain aging in evolutionary terms. One of these hypotheses is antagonistic pleiotropy (Williams, 1957).

Although controversial (Rose et al., 2002), antagonistic pleiotropy may offer some interesting ramifications with respect to telomere dynamics. The hypothesis was originally conceived to explain the role of genes in aging, while giving credence to a central evolutionary principle, i.e. the declining force of natural selection with age. Antagonistic pleiotropy suggests that genes favored by natural selection because they provide robustness and reproductive advantage during early life may in later life cause age-related diseases i.e. unsuccessful aging (Williams, 1957). If genes contribute to the span of human life, subsets of genes may determine the biology of successful and the pathobiology of unsuccessful aging, for which telomeres can be a useful biomarker, in at least two ways.

First, the concurrent interplay between growth and telomere dynamics may reflect the dichotomous actions of classes of genes throughout the life span. During early life, these genes may facilitate robustness through enhancing somatic cell proliferation, while in later life the same genes may amplify age-related disorders and accelerate physiological decline exactly through the same modes of action exerted during early life. For instance, host defense mechanisms against pathogens largely depend on generating a robust inflammatory response. Classes of variant genes that promote a strong inflammatory response (Kiechl et al., 2002) would support good health and hence, fecundity during the reproductive years. Yet the benefits provided by the these genes may be overshadowed in later life by the cumulative and deleterious effect of the inflammatory response on the vasculature, resulting in accelerated atherosclerosis (Dzau, 2001; Ridker et al., 2002). The rates of telomere erosion in WBCs or subsets of WBCs

throughout different phases of life span in different individuals may provide valuable information in this regard.

Second, it is doubtful that in most human somatic tissues the involvement of telomeres in aging would be through a process of replicative senescence, as has been suggested for instance for adrenal cells (Yang et al., 2001). However, rapid proliferation that supports robust growth in early life may accelerate telomeric erosion, leading to the premature activation/silencing of genes that promote aging in later life. In principle, such a possibility can be explored by monitoring telomere erosion.

2. Conclusions

The use of mortality rate as an index of aging hardly reflects the diverse causes of mortality among individuals. Modern humans are afflicted in their old age by a host of disorders that arise from the breakdown of metabolic pathways, leading to dysfunctions of different tissues and organs. These disorders may be attributed to families of genes that have survived the throes of evolution to exert their effects not only in early development but also in later life. When the causes of mortality are factored in calculating the mortality rate associated with aging, it is apparent that individuals who manifest age-related disorders such as cardiovascular diseases, diabetes and cancer, i.e. subjects expressing unsuccessful aging, show a mortality rate peak at a younger age than their peers. This suggests that unsuccessful aging is largely a manifestation of an early onset of aging or an accelerated aging. From this standpoint, the ability to calculate the lifetime risk of developing a disease of aging, e.g. cardiovascular disease (Lloyd Jones et al., 1999, 2002), during an individual's remaining life span provide a better understanding of human aging. The unresolved issue, however, is whether the dynamics of telomeres in vivo may provide important and heretofore missing information about the role of proliferation and turnover of somatic cells during different phases of lifespan in the individual's lifetime risk of premature expression of age-related diseases.

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