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Review

Aging, telomeres, and atherosclerosis

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Abstract

Although the level and pace of population aging display high geographical variability, virtually all countries have been experiencing growth in their elderly population, particularly in developed nations. Because aging is a major risk factor for atherosclerosis and associated disease, it is of up most importance to unravel the molecular mechanisms involved in vascular aging. Telomeres are specialized DNA-protein structures located at the ends of eukaryotic chromosomes whose length is progressively reduced in most somatic cells during aging. It is accepted that telomere exhaustion contributes to organismal ageing at least by impairing cell proliferation and viability. An emerging question is whether telomere erosion contributes to atherosclerosis. Here we discuss recent advances on the molecular control of telomere length in vascular cells, as well as animal and human studies that address the role of telomeres in vascular pathobiology. Although the interrelationships between telomere length and cardiovascular disease appear obvious, a chief question that remains unanswered is whether telomere ablation is cause of vascular injury or a surrogate phenomenon.

Keywords: Aging; Telomeres; Telomerase; Atherosclerosis; Hypertension; Diabetes

1. Telomere biology

Telomeres are specialized DNA-protein complexes located at both ends of eukaryotic chromosomes. Functional telomeres are required to prevent the recognition of chromosomal ends as double-stranded DNA breaks, thus preserving genome integrity and stability [1,2]. As depicted in Fig. 1A, telomeric DNA consists of non-coding double-stranded repeats of G-rich tandem sequences (TTAGGG in humans) that extend several thousand base pairs and end in a 3′-overhang (G-strand overhang). The synthesis of telomeric DNA requires the activity of specialized telomere-associated proteins (i.e., telomerase, TRAF1, TRAF2, Ku86, etc). The enzyme telomerase has a catalytic telomerase reverse transcriptase (TERT) component and a telomerase RNA (Terc) that provides a template for new telomeric DNA synthesis.

Telomere protection depends on several factors, including the precise composition of telomere-associated proteins, the level of telomerase activity, and telomere length itself [1,2]. Cells with sufficiently long telomeres do not require telomerase activity, but lack of telomerase activity in cells with critically short telomeres leads to chromosomal fusions, replicative senescence, and apoptosis (Fig. 1B). Telomerase expression and activity and telomere length are regulated in a tissue-specific and developmental manner in several species, including humans [3–6]. In general, these parameters are greater during embryonic development and become low or undetectable after birth, although significant differences in adult tissues have been reported. For instance, human telomeric DNA shortens at an estimated rate of 29–60 base pairs per year (bp/year) in liver, renal cortex and spleen, but telomere length is maintained in cerebral cortex [7]. Notably, human prema-

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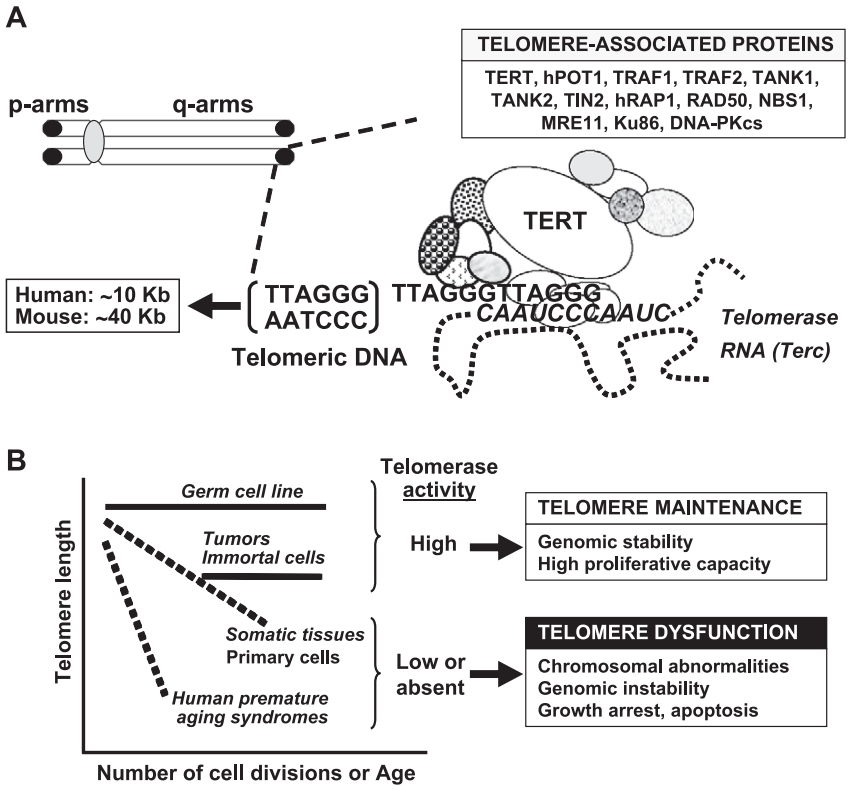

Fig. 1. Telomere integrity and cellular homeostasis. (A) Left: Schematic showing telomeres (black circles) at both ends of chromosomes. Right: Enlargement of the telomere showing the human telomeric DNA tandem repeat sequence, the telomeric RNA component (Terc), the catalytic telomerase reverse transcriptase (TERT) subunit, and additional telomerase-associated proteins. (B) Telomere attrition occurs progressively in somatic cells with each mitotic cycle during normal aging and passage in culture, due in part to low or absent telomerase activity. In contrast, high telomerase activity in germ and tumor cells allows the maintenance of telomere integrity and an extended proliferative capacity. Accelerated telomere erosion is a characteristic of several human premature aging syndromes (i.e., Werner syndrome, ataxia telangectasia, dyskeratosis congenita).

ture aging syndromes (i.e., Werner syndrome, ataxia telangectasia, dyskeratosis congenita) are characterized by an accelerated rate of telomere attrition (Fig. 1B). Progressive telomere shortening in cell culture and during aging of the whole organism is a characteristic of most adult somatic cells, which exhibit low or absent telomerase activity [8–10]. Of note in this regard, human TERT (hTERT) is alternatively spliced in specific patterns by different tissue types during development, and this mechanism often leads to the expression of hTERT protein lacking functional reverse transcriptase domains [11]. In contrast to adult somatic cells, the extended proliferative capacity of germ and tumor cells correlates with the maintenance of high telomerase activity and long telomeres. The importance of telomere integrity for high rate of cellular proliferation is further emphasized by TERT gene transfer experiments, which result in reduced replicative senescence and extended lifespan of numerous cell types, including smooth muscle cells (SMCs) and endothelial cells (ECs) (Table 1). By comparing the chronological changes in the expression of cell cycle and apoptosis-related genes in hTERT-transduced human normal fibroblasts and ECs, Kumazaki et al. [12] suggested that cell-type specific differential gene expression after telomerase activation may be important to acquire telomere-maintenance capacity and immortality.

Telomere length displays individual differences in both rodents [5,6] and humans [7,13–15]. High variability of telomeric DNA length in white blood cells (WBCs), umbilical artery and skin from donor newborns independently of gender suggests that genetic and environmental determinants that start exerting their effect during embryonic development are key determinants of telomere length [13]. Further support to the notion that telomere size is familial has arisen from human studies in twins [14,16]. By measuring terminal restriction fragment (TRF) length in WBC DNA taken from individuals from a family-based cohort, Nawrot et al. [17] concluded that inheritance of telomere length is linked to X chromosome.

2. The importance of telomeres in vascular pathobiology

In the next sections, we will discuss tissue culture, animal and human studies that highlight the importance of telomeres in vascular pathobiology, with special emphasis on recent insights into the mechanisms that alter telomere homeostasis in response to several atherogenic stimuli and

Table 1
Cell culture studies implicating telomere length and telomerase in vascular pathobiology

Cell type	Main findings	Refs.
Smooth muscle cell (SMC)	Hypoxia-induced telomerase activation in human SMCs correlates with increased cellular proliferation	[55]
	Telomerase activity correlates with proliferation of primary SMCs, and its inhibition attenuates hyperplastic growth	[56,81]
	hTERT forced overexpression extends the lifespan of rat SMCs	[80]
Endothelial cell (EC)	Telomere attrition correlates with limited proliferative capacity of passaged human ECs	[60,82]
	Telomerase ectopic overexpression or inhibition affect the lifespan of human aortic ECs	[58,83]
	Constitutive hTERT expression enhances the regenerative capacity of endothelial progenitor cells	[54]
	FGF-2, but not VEGF, upregulates telomerase activity and delays the onset of senescence in HUVECs	[51,52]
	Estrogen activates the PI3K/Akt pathway in human ECs, and Akt activation upregulates human telomerase activity; in contrast, PI3K inhibition and dominant negative Akt mutant significantly reduce telomerase activity in EC cultures	[29,31,32]
	Estrogen induces nitric oxide production and telomerase activity in vascular ECs.	[29,30]
	Oxidized low density lipoproteins diminish Akt and telomerase activity in ECs	[32]
	Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human ECs	[35]
	Antioxidants inhibit nuclear export of TERT and delay replicative senescence of human ECs	[39]

conditions (i.e., estrogens, oxidative stress, hypertension and diabetes) (Table 1 and Fig. 1). Since collateral vessel formation supports the restoration of blood flow into ischemic territories and development of new *vasa vasorum* enhances atherosclerosis [18,19], we will also discuss the role of telomeres on neovascularization. The importance of telomeres on cardiac pathobiology has been comprehensively discussed elsewhere [20,21].

2.1. Telomeres and estrogens

Indirect effects on lipoprotein metabolism and direct actions on vascular ECs and SMCs are thought to contribute to the cardioprotective effects of estrogens in premenopausal women [22–25]. It is noteworthy that human and animal studies have shown higher telomerase activity and a decelerated rate of age-dependent telomere exhaustion resulting in greater telomere lengths in females than in males [4,6,16,17,26,27]. These sex differences might be directly related to estrogen-dependent activation of endothelial telomerase via phosphoinositol 3-kinase (PI3K)/Akt and nitric oxide signaling. First, estrogen upregulates hTERT mRNA, and this correlates with direct and indirect effects on the hTERT promoter (specific binding of 17β-estradiol to an imperfect palindromic estrogen-responsive element, and 17β-estradiol-dependent induction of c-Myc/Max binding to E-boxes, respectively) [28]. Second, nitric oxide production may contribute to telomerase activation in vascular ECs [29,30]. Third, treatment of human ECs with estrogen activates the PI3K/Akt pathway [29], which in turn leads to hTERT phosphorylation and activation [31]. In contrast, either overexpression of dominant negative Akt or PI3K inhibition attenuates telomerase activity in ECs, [32] and Akt inactivation by proatherogenic oxidized low density lipoproteins impairs telomerase activity in ECs [32]. Collectively, these studies suggest that a positive effect of PI3K/Akt on telomerase expression and activity may contribute to the maintenance of EC integrity and function. Contrary to this notion, Miyauchi et al. [33] recently reported that constitutive activation of Akt promotes senescence-like arrest of human EC growth via a p53/p21-dependent pathway. Additional studies are thus required to clarify the links between telomere function, PI3K/Akt signaling and EC pathobiology.

2.2. Telomeres and oxidative stress

Accumulation of oxidative damage is thought to play an important role in aging and associated diseases [34]. Mounting evidence implicating oxidative stress in telomere dysfunction includes the following: (1) Chronic oxidative stress induces a rapid and sustained decrease in TERT activity and accelerates telomere attrition in human umbilical vein ECs (HUVECs) [35]; (2) maximum levels of glutathione coincide with a peak of telomerase activity in proliferating 3T3 fibroblasts; moreover, glutathione depletion decreases by 60% telomerase activity, and restitution of glutathione levels restores telomerase activity [36]; (3) age-dependent telomere shortening in HUVECs is slowed down by Asc2P, and oxidation-resistant derivative of vitamin C which reduced by 53% the level of proatherogenic reactive oxygen intermediates [37]; (4) oxidized low density lipoproteins inhibit EC telomerase activity [32]; (5) oxidative stress induced in human ECs by exposure to H_2O_2 leads to translocation of both endogenous and overexpressed hTERT from the nucleus into the cytosol via Src kinase family-dependent phosphorylation of hTERT tyrosine 707, which reduces the antiapoptotic capacity of TERT; [38] furthermore, reduction of intracellular reactive oxygen species formation by the antioxidant *N*-acetylcysteine prevented mitochondrial damage and delayed nuclear export of TERT protein, loss of TERT activity and the onset of replicative senescence [39]; and (6) formation of 8-oxo-7,8-dhydro-2′-deoxyguanosine at the GGG triplet in the telomeric DNA sequence may be a mechanism facilitating telomere shortening induced by oxidative stress [40].

2.3. Role of telomeres in vascular pathobiology: lessons learnt from cell culture and animal studies

The Terc-deficient mouse model has been a valuable tool to investigate the impact of telomere ablation at the organismal level [41–48]. The breeding of successive generations of Terc-null mice is needed to reach critically short telomeres that lead to abnormal chromosome end-to-end fusions and symptoms of premature aging and disease, such as infertility, graying of hair, alopecia, impaired wound healing, small intestine and spleen atrophy, reduced proliferation of T and B lymphocytes, and hematopoietic disorders. Furthermore, late-generation Terc-null mice display reduced lifespan. We will discuss in the next sections studies with cultured cells, Terc-null mice, spontaneously hypertensive rats and other animal models that link telomeres and vascular pathobiology (Table 1 and Fig. 2).

2.3.1. Atherosclerosis

Our recent studies using genetically modified mice suggest that telomere shortening protects against atherosclerosis [48]. We found that late-generation mice doubly deficient for Terc and apolipoprotein E (Terc/apoE-KO) have shorter telomeres and are protected from diet-induced atherogenesis compared to atherosclerosis-prone apoE-null counterparts with an intact Terc gene and longer telomeres, in spite of comparable hypercholesterolemia. Telomere exhaustion markedly inhibited the proliferative capacity of cultured Terc/apoE-KO lymphocytes and macrophages stimulated with several mitogens. Thus, telomere ablation might attenuate atherogenesis by limiting leukocyte proliferation. It remains to be established whether telomere attrition affects additional events involved in atherogenesis, such as the interaction between blood circulating leukocytes and ECs, transendothelial migration of leukocytes, synthesis of inflammatory mediators, and cellular proliferation, migration, and apoptosis.

An important issue when interpreting the atheroprotective role of telomere exhaustion in hypercholesterolemic Terc/apoE-KO mice is that human aging is associated with telomere erosion in most somatic cells [9,10], yet atherosclerosis is more prevalent within the elderly. These seemingly conflicting findings might be reconciled accepting that accumulation of cellular damage imposed by prolonged exposure to cardiovascular risk factors may ultimately prevail over protective mechanisms such as telomere shortening. The evidence linking telomere length and human atherosclerosis is discussed below (see Section 2.4.1).

2.3.2. Neovascularization

Proliferation of *vasa vasorum* promotes atherosclerosis [18]. On the other hand, therapeutic neovascularization is essential for the restoration of blood flow into ischemic territories in the adult organism, which depends on the development of new collateral vessels from established vascular networks (angiogenesis) and on de novo vessel formation by endothelial progenitor cells (vasculogenesis) [19]. Using an experimental model of limb ischemia, Rivard et al. [49] demonstrated an impairment of angiogenesis in old vs. young rabbits. They also showed age-dependent diminished expression of the angiogenic cytokine vascular endothelial growth factor (VEGF), and old rabbits exposed to exogenous VEGF exhibited a similar increase in blood pressure ratio, angiographic score, and capillary density than did young counterparts. Thus, VEGF downregulation might be critical for age-dependent impairment of angiogenesis in response to ischemia, and this may result from reduced activity of the transcription factor hypoxia-inducible 1 (HIF-1) [50]. Remarkably, whereas both angiogenic cytokines VEGF and fibroblast growth factor-2 (FGF-2) elicited a

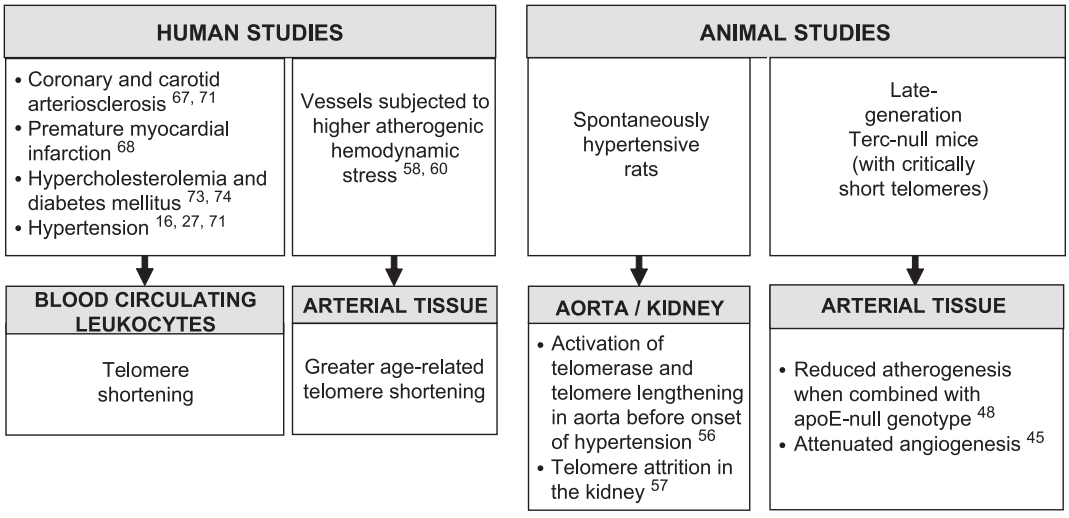

Fig. 2. Telomeres and telomerase in atherosclerosis and hypertension. Human (left) and animal (right) studies that have implicated telomere length and telomerase activity in atherosclerosis and hypertension are summarized. Successive generations of Terc-null mice are necessary to reach critically short telomeres and associated diseases. Reference numbers are shown.

mitogenic response in cultured HUVECs, only FGF-2 induced the upregulation of hTERT mRNA and enzymatic activity and delayed the appearance of a senescent phenotype [51,52]. Because of these differences, it would be interesting to compare in old rabbits the angiogenic response elicited by exogenous FGF-2 and VEGF.

Overexpression of hTERT in human dermal microvascular ECs (HDMECs) augments their capacity to form more durable microvascular structures when subcutaneously xenografted in severe combined immunodeficiency mice [53]. Similarly, hTERT gene transfer into human endothelial progenitor cells improves their proliferative and migratory activity, enhances survival, and augments neovascularization when applied in a murine hindlimb ischemia model [54].

Recruitment of SMCs and pericytes into new capillaries composed by a monolayer of ECs is important for their stabilization and maturation into fully functional vessels. Hypoxia is a major angiogenic stimulus that induces TERT protein expression and phosphorylation in cultured SMCs [55]. Telomerase inhibition shortened the life span of hypoxic cultures, and constitutive TERT expression extended life span under normoxia, suggesting that hypoxia-mediated telomerase activation promotes long-term SMC growth. It remains to be established if chronic hypoxia can induce endothelial telomerase activity.

Telomere exhaustion in late generation Terc-null mice leads to a sharp decrease in angiogenesis in both Matrigel implants and murine melanoma grafts, diminished tumor cell proliferation, increased tumor cell apoptosis, and a lower tumor growth rate [45]. Given the data implicating neointimal angiogenesis as a mechanism contributing to atheroma growth [18], it will be instructive to compare neointimal vasa vasorum density in late-generation Terc/apoE-KO mice with short telomeres and apoE-null counterparts with intact telomeres.

2.3.3. Hypertension

In the aorta of spontaneously hypertensive rats, but not in other tissues, telomerase is activated before the onset of hypertension, and telomeres are lengthened both in vivo and in cultured SMCs from these animals [56]. Down-regulation of telomerase by TERT antisense RNA delivery arrested the increased proliferation of spontaneously hypertensive rat vascular SMCs and induced apoptosis by a mechanism that can be reversed by p53 overexpression and worsened by lowering p53. It was concluded that selective TERT activation and subsequent telomere lengthening in aortic medial SMCs are the driving force for the imbalance between cell proliferation and apoptosis that ultimately results in the vascular remodeling seen in genetic hypertension. Hamet et al. [57] observed in the kidney of spontaneously hypertensive rats a transient hyperplasic response during the first 2 weeks of postnatal life that was absent in age-matched normotensive controls. Because shorter telomeres are detected in the kidney of spontaneously hypertensive rats at all ages examined, the authors suggested that kidney cells from these animals are subjected to increased turnover, potentially leading to their accelerated aging.

2.4. Role of telomeres in vascular pathobiology: evidence from human studies

2.4.1. Atherosclerosis

By inducing replicative senescence, age-dependent telomere erosion may contribute to progressive endothelial dysfunction and atherosclerosis. Indeed, a characteristic senescent phenotype is observed in the endothelium of atherosclerotic lesions [58]. Of note, overexpression of a dominant-negative mutant of telomere repeat binding factor 2 (TRF2) induces senescence in human aortic EC cultures, and TERT transduction can prevent replicative senescence of these cells [58]. Both telomere shortening and increased frequency of aneuploidy is observed in ECs from the aged abdominal aorta [59]. Remarkably, telomeric DNA shortening occurs at a greater rate in the endothelium of iliac arteries vs. iliac veins (102 vs. 47 bp/year, respectively), and age-dependent intimal telomere attrition is greater in the iliac artery compared to the internal thoracic artery (147 vs. 87 bp/year, respectively), [60] a vessel subjected to a reduced amount of hemodynamic stress. Okuda et al. [61] also reported increased age-dependent telomere ablation in both the intima and media of the distal vs. proximal abdominal aorta, and they found an inverse correlation between atherosclerotic grade and telomere length (although this relationship was not statistically significant after adjustment for age). Taken together, these studies suggest a higher rate of telomere shortening in aged vascular beds with increased shear wall stress and enhanced cellular turnover.

Circulating leukocytes are key players during atherosclerosis [62–65]. Recent studies have compared telomere length in WBCs from healthy controls and cardiovascular patients. Patients with vascular dementia, a disorder that is frequently associated with cerebrovascular atherosclerosis and stroke, have significantly shorter telomeres in WBCs compared with three age-matched control groups, namely cognitively competent patients suffering from cerebrovascular or cardiovascular disease alone, patients with probable Alzheimer's dementia, and apparently healthy control subjects [66]. Likewise, leukocyte average telomere length in 10 patients suffering severe coronary artery disease (CAD) was significantly reduced compared with 20 controls with normal coronary angiograms after adjustment for age and sex [67]. In a larger study including 180 controls and 203 cases of premature myocardial infarction (MI), age-and sex-adjusted mean TRF length of controls was significantly larger than that of patients, and subjects with shorter than average telomeres had between 2.8- and 3.2-fold higher risk of MI [68]. Furthermore, analysis of telomere length in

blood DNA from 143 normal unrelated individuals over 60 years of age disclosed an association between shorter telomeres and poorer survival that was partly attributed to a 3.18-fold mortality rate from heart disease and a 8.54-fold higher mortality rate from infectious disease [69]. Taken together, these human studies establish a link between telomere shortening in WBCs and cardiovascular disease. Whether telomere ablation in these scenarios is a surrogate phenomenon or a mediator or injury remains to be established (see Section 4).

2.4.2. Hypertension and diabetes

Hypertensive patients are more prone to atherosclerotic lesions and acute ischemic events than normotensive individuals [70]. Analysis of 49 twin pairs (38 males and 60 females between the age of 18 and 44 years) revealed a positive correlation between WBC TRF and diastolic blood pressure [16]. Because TRF length and systolic blood pressure were inversely associated, telomere length seems to negatively correlate with pulse pressure. Notably, the link between TRF length and pulse pressure was independent of gender, and both parameters appeared highly heritable. Benetos et al. [27] also investigated WBC telomere length and blood pressure parameters that are associated with stiffness of large arteries (pulse pressure and pulse wave velocity) in individuals who were not under antihypertensive medications (120 men, 73 women, mean age of 56±11 years). While telomere length negatively correlated with age in both sexes, multivariate analysis showed that telomere shortening significantly contributes to increased pulse pressure and pulse wave velocity only in men. In both studies, women showed age-adjusted longer telomeres, suggesting that biological aging is slowed down in women. More recently, Benetos et al. [71] examined the relationship between WBC telomere length and carotid artery atherosclerosis in 163 treated hypertensive men who were volunteers for a free medical examination. They found that telomere length was shorter in hypertensive men with carotid artery plaques vs. hypertensive men without plaques (8.17±0.07 vs. 8.46±0.07 kb; $p<0.01$), and multivariate analysis revealed that, in addition to age, telomere length significantly predicts the presence of carotid artery atherosclerosis.

The prevalence of both microvascular and macrovascular disease is significantly increased in diabetic patients [72]. Telomere length in WBCs from insulin-dependent diabetes mellitus patients is reduced compared with age-matched nondiabetic subjects [73]. This parameter was similar in non insulin-dependent diabetes mellitus patients and nondiabetic controls, suggesting that telomere erosion only occurs in a subset of WBCs that participate in the pathogenesis of insulin-dependent diabetes mellitus. Further support implicating telomere exhaustion as a mechanism contributing to coronary atherosclerosis under some circumstances of metabolic disorders arises from the observation that hypercholesterolemic and diabetic CAD patients display shorter telomeres in peripheral blood mononuclear cells than healthy controls [74].

2.4.3. Neovascularization

The importance of telomerase in human angiogenesis is highlighted by the progressive induction of hTERT mRNA expression in human ECs of newly formed vessels within tumors [75]. Endothelial hTERT expression was observed in 29%, 56% and 100% of low-grade astrocytomas, anaplastic astrocytomas and advanced glioblastomas multiforme, respectively. While the proliferation rate and hTERT mRNA expression are dissociated in human ECs from low-grade and anaplastic astrocytomas, high proliferation rate and hTERT mRNA level positively correlated in glioblastomas multiforme. Remarkably, hTERT mRNA and protein expression and telomerase activity are induced in EC cultures exposed to diffusible factor(s) produced by human glioblastoma cells [76].

3. Telomerase gene transfer for therapeutic revascularization

By analyzing the offspring obtained by mating heterozygous Terc+/− mice and late-generation Terc-null mice, which have short telomeres, unstable chromosomes and signs of premature aging, Samper et al. [77] demonstrated that critically short telomeres can become fully functional by restoration of telomerase. Because age-dependent telomere erosion may compromise the reestablishment of adequate blood supply into ischemic territories by limiting de novo vessel formation (see Section 2.3.2), telomerase gene transfer appears an attractive strategy to boost therapeutic neovascularization. It has been shown that ex vivo expanded human endothelial progenitor cells enhance therapeutic neovascularization in animals, [78] and in vivo transplantation of hTERT-transduced endothelial progenitors increased capillary density and limb salvage in a murine model of hindlimb ischemia [54]. Nonetheless, telomere-independent barriers might limit the transplantation potential of murine hematopoietic stem cells, since TERT overexpression in these cells did not extend transplantation capacity in spite of preventing telomere loss during serial transplantation [79].

McKee et al. [80] have provided evidence that hTERT transduction may be an appropriate strategy for the production of tissue-engineered human arteries for bypass surgery. Compared with control cells, passaged human aortic SMCs overexpressing hTERT maintained telomere length, disclosed extended lifespan, and retained a normal morphology and a differentiated, non-malignant phenotype at late-passage. Remarkably, engineered vessels containing HUVECs and hTERT-transduced SMCs showed improved cellular viability and were mechanically and architecturally superior to vessels generated from non-transduced SMCs.

4. Concluding remarks

By imposing chromosome abnormalities, replicative senescence, and apoptosis, progressive telomere shortening in somatic cells is thought to contribute to aging and associated disorders. Both animal and human studies suggest that the maintenance of telomere integrity is essential for effective neovascularization, and "telomerization" of endothelial progenitors by means of hTERT gene transfer may be an efficient strategy to boost therapeutic neovascularization of ischemic tissues after acute infarction. Regarding the role of telomeres in atherosclerosis, it has been shown that telomeres are shorter in human arterial tissue from atherosclerosis-prone vs. atherosclerosis-resistant vascular beds, as well as in WBCs from hypertensive, diabetic and CAD patients compared to unaffected controls. Thus, telomere exhaustion may be a primary abnormality that renders the organism more susceptible to atherogenic stimuli. Challenging this notion, atherosclerosis induced by dietary cholesterol is significantly reduced in Terc/apoE-KO mice with critically short telomeres compared to apoE-null counterparts with intact telomeres, in spite of comparable hypercholesterolemia. These seemingly contradictory findings may reflect profound differences in telomere pathobiology between humans and mice. Alternatively, because SMC and leukocyte proliferation is a characteristic of atherosclerosis and telomere shortening is greater in highly proliferative cells, reduced telomere length in human atherosclerotic tissue and WBCs from hypertensive, diabetic and CAD patients may be a surrogate phenomenon. Thus, establishing conclusively whether telomere ablation is cause or consequence of vascular injury will require prospective epidemiological studies to assess if newborns with shorter telomeres are more prone to cardiovascular disease in adulthood independently of known cardiovascular risk factors. Of note in this regard, a high degree of individual variability is observed in human telomere length, which seems to be controlled by both genetic and environmental factors. In addition to epidemiological studies, further basic research is needed to assess whether genetic and environmental cardiovascular risk factors affect telomerase activity and/or telomere length, and to gain mechanistic insight into the role of telomerase and additional telomere-associated proteins in cardiovascular pathobiology.

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