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Telomere biology in cardiovascular disease

Summary

Advanced age brings about significant changes to cardiovascular physiology, and is an independent risk factor for the development of atherosclerosis. The basis for this association remains unclear, but it has been suggested that atherogenesis may share common mechanisms with the ageing process. Ageing at the cellular level leads to a condition known as replicative senescence, which is triggered by the shortening of chromosomal telomeres during repeated cell division. Senescent endothelial cells show a number of features, which could contribute to the initiation or progression of the atherosclerotic plaque, such as loss of regenerative capacity and increased expression of pro-atherogenic proteins. This review will outline the current understanding of telomere function and summarise the evidence supporting a role for senescence-driven pathophysiology of vascular cells in age-related cardiovascular disease. This will include published work from vascular cell culture, animal experiments and observational studies in humans.

Zusammenfassung

Mit zunehmendem Alter stellen sich beträchtliche Veränderungen der kardiovaskulären Physiologie ein. Zudem ist das Alter ein wichtiger unabhängiger Risikofaktor für die Entwicklung atherosklerotischer Erkrankungen. Die Ursachen dieser Zusammenhänge sind unbekannt, es wird aber vermutet, dass gemeinsame Mechanismen der Atherogenese und dem Alterungsprozess zugrunde liegen könnten. Auf zellulärer Ebene führt die Alterung zur sogenannten replikativen Seneszenz, ein physiologischer Zustand, welcher durch die Verkürzung der Telomere (die Enden der Chromosomen) im Verlaufe wiederholter Zellteilungen herbeigeführt wird. Seneszente Endothelzellen weisen charakteristische Veränderungen auf, welche zur Entstehung oder Progression der atherosklerotischen Plaque beitragen könnten, so zum Beispiel der Verlust der regenerativen Kapazität oder die Expression von pro-atherogenen Proteinen. In dieser Übersichtsarbeit wird die Struktur und Funktionsweise des Telomers erläutert. Zudem wird die Evidenz zusammengefasst, welche für eine Beteiligung der seneszenz-assoziierten Pathophysiologie vaskulärer Zellen in der Entstehung von altersabhängigen kardiovaskulären Erkrankungen sprechen. Dabei wurden sowohl publizierte Arbeiten mit zell- und tierexperimentellen Modellen, als auch klinische Assoziationsstudien berücksichtigt.

Ageing and atherosclerosis

In humans, the ageing process brings about a wide array of changes to cardiovascular physiology, and even in the absence of established risk factors ageing is associated with major cardiovascular morbidity and mortality [1]. Advanced age is associated with hypertension [1], endothelial cell dysfunction [2, 3], impairment of angiogenesis [4] and a decrease in antithrombotic activity [5]. Furthermore, ageing itself is one of the strongest independent risk factors for the development of atherosclerosis [1, 2]. The basis for this association remains unclear, but it has been proposed that atherosclerosis may share common biological mechanisms with the ageing process [6]. This review will summarise the evidence supporting a role for telomere-driven replicative senescence, one of the intrinsic cellular mechanisms implicated in the ageing process, in the development of age-related cardiovascular disease.

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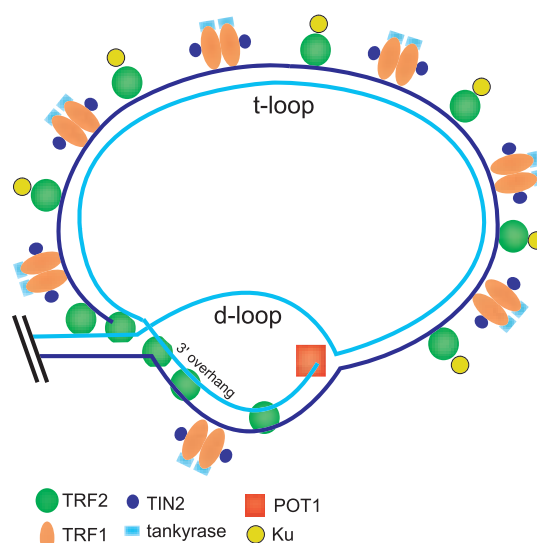
Telomeres: the mitotic clock

Replicative senescence is a permanent non-dividing state, which ensues in most somatic cells following a pre-determined number of cell divisions [7]. Under ideal cell culture conditions, human somatic cells proliferate for up to 40–60 population doublings (ie 40–60 mitoses per cell) before entering senescence [8]. Senescent cells are blocked in the G1 phase of the cell cycle and thus cannot replicate, but remain viable and are metabolically active. However, senescent cells differ from their younger ancestor cells in regard to morphological, gene expression and functional characteristics. Replicative senescence is brought about by a progressive shortening of telomeres throughout a cell's replicative life span [9]. Telomeres build the physical ends (caps) of chromosomes. They consist of non-coding, serial repeats of the nucleotide sequence TTAGGG, which in humans vary in length between 5000 and 15 000 base pairs, and end in a 3' single-stranded DNA overhang. This DNA segment is complexed with a number of specialized telomere-associated proteins. Current evidence suggests that these proteins enable the telomeric DNA double helix to fold back upon itself to form a special loop structure (fig. 1) [10]. According to this model, the 3-dimensional integrity of this so-called "T-loop", in which the 3' single-strand overhang is thought to displace the complementary DNA-strand of the double helix ("D-loop") [11] and is thus "tucked away", is a prerequisite for the maintenance of cellular replicative capacity. Would chromosomes end with a "free" open tail, they would falsely be identified by the cellular DNA damage control machinery as a DNA break, which would result in the cell being blocked from entering the cell cycle. Apart from this chromosome capping function, telomeres play an important role in the maintenance of chromosome stability during DNA replication, as well as chromosomal positioning and segregation during mitosis [12].

The progressive shortening of telomeres with each cell division occurs at a rate of about 25–200 base pairs (bp) per mitosis. This is a direct result of the so-called "end-replication problem", which describes the inability of conventional DNA polymerases to replicate the 3' termini of the template strands, resulting in incomplete copying [13]. Thus, the presence of telomeres prevents the erosion of coding DNA sequences at the ends of the chromosomes during DNA replication. Telomere erosion with each cell division is cumulative, and a large body of evidence now suggests that once a critical degree of telomere shortening is reached, the telomere is unable to maintain its 3-dimensional structure, which in turn is recognised by the cell-cycle machinery as a signal to block further replication (fig. 2). Thus, telomere length appears to act as a mitotic counting device, or "replicometer", which counts cell divisions and limits replicative capacity by triggering entry into senescence [9].

Vascular cell senescence in vascular ageing and atherosclerosis

In vivo, the vascular endothelium is known to undergo a low cellular turnover [14]. However, during episodes of angiogenesis or following vascular injury, cells in the vessel wall may be required to carry out a considerable number of cell divisions. It is also known that endothelial cell replication rates are increased at "atherosclerosis-prone areas" such as vascular branching points [15], most likely representing a response of the endothelium to the chronic stress of shear and stretch at these sites [16]. This suggests that, in vivo, as chronological age advances, areas with high endothelial cell turnover could be increasingly covered by clusters of senescent cells. Interestingly, endothelial cells undergoing senescence in culture demonstrate a number of characteristic changes, which are typically also found in atherosclerotic lesions in vivo. These include both changes in morphology (an increase in

Figure 1

Model of the 3-dimensional superstructure of the human telomere. At the end of the chromosome, telomeric DNA folds back upon itself to form the t-loop (telomere or terminal loop). The t-loop is thought to be stabilised by the 3' single-strand end of the telomere ("overhang") displacing the complementary DNA-strand of the double helix (d-loop = displacement loop), it thus being "tucked away" and hidden from recognition by the DNA damage machinery. A number of telomere-associated proteins play essential roles in maintaining the integrity of this 3-dimensional structure and also contribute to telomere length regulation. Figure adapted from [80].
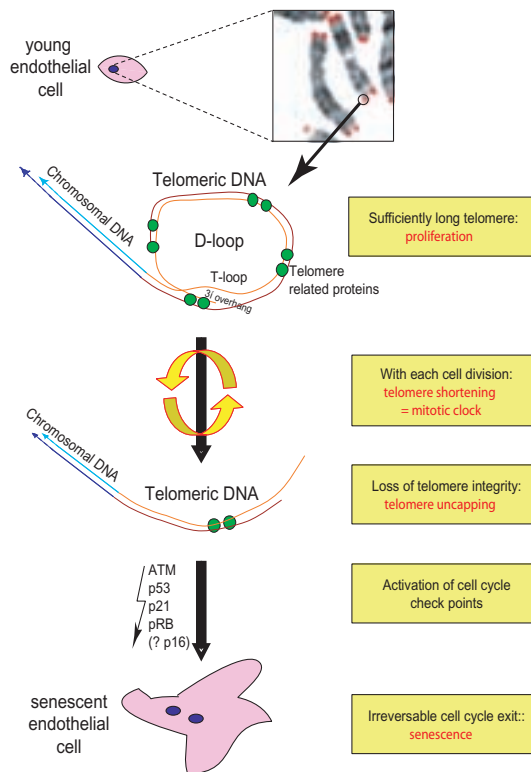
Figure 2

Telomere mechanism of cellular senescence. Senescence ensues in normal somatic cells following a predetermined number of cell divisions. Due to the inability of conventional DNA polymerases to completely replicate the 3' termini of the template strands, telomeric DNA shortens with each round of cell division. Once a critical degree of telomere shortening is reached, the 3-dimensional integrity of the telomere is lost, which is recognised by the cell-cycle machinery as a signal to permanently block further replication.


Figure 3

Biomarkers of senescence in human endothelial cells. A, B. Bright field photomicrograph showing young and senescent cultured human umbilical vein endothelial cells (HUVEC) stained for senescence-associated β-galactosidase (SA-β-gal) activity (135× magnification). Note the lack of blue granula in the young cells, while the senescent cells display in part intense blue staining. Note also the increased cell size and polyploidy of senescent cells.
C, D. Same cultures as in A and B, but stained with acridine orange identifying lysosomes in orange (Fluorescence micrograph 225× magnification). Note the impressive increase in lysosomal content in the senescent cultures.
E, F. Metaphase spreads of young and senescent HUVEC. Fluorescence in situ hybridisation with a telomeric probe (1000× magnification). Note the increased telomere signal (red) at the ends of each chromosome arm in the young cell compared to the senescent cell.
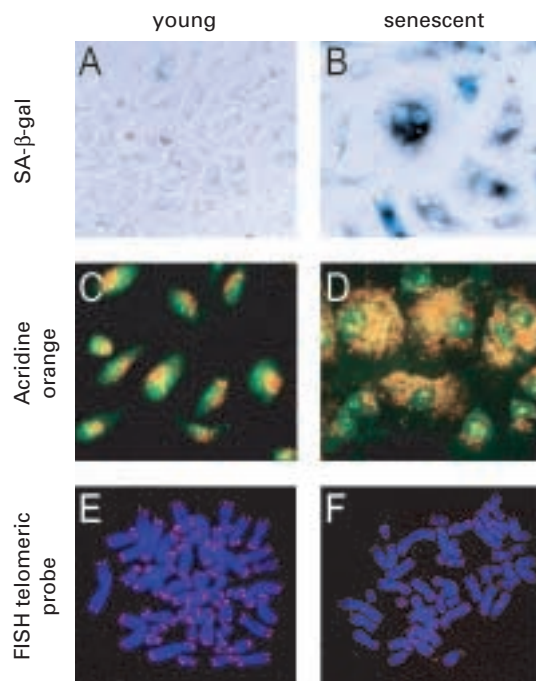
cell size, the presence of multiple nuclei, increased vacuolisation) [17, 18] and gene expression. Thus, both the atherosclerotic plaque and senescent endothelial cells overexpress interleukin-1α [19, 20], plasminogen activator inhibitor-1 [5, 21], and the surface molecule ICAM-1 [22, 23]. More compelling evidence suggesting a role for senescence in vascular pathology has become available with

the discovery of a more reliable biomarker of senescent cells, the so-called "senescence-associated β-galactosidase activity" (SA-β-gal) [24], which has subsequently been used widely in the scientific community. This cytochemical assay takes advantage of the propensity of senescent cells to vastly increase their number of lysosomes, and thus also their content and activity of the endogenous lysosomal enzyme β-galactosidase [25]. The assay distinguishes senescent from non-senescent cells by staining at a suboptimal pH of 6 (instead of pH = 4), at which only the senescent cells have sufficient β-gal activity to convert the colourless enzyme substrate to the visible blue cleavage product [25] (fig. 3A–D). The SA-β-gal assay has been shown to be an excellent biomarker of vascular cells in vitro [26], and was subsequently used to demonstrate the emergence of senescent vascular cells following vascular injury in vivo [27]. In these experiments, rabbit carotid arteries were injured once or twice by balloon angioplasty at three-week intervals, and then histologically examined after SA-β-gal staining. In contrast to the uninjured contralateral vessels, in which no senescent cells were found, the neo-intima of the treated vessels contained isolated senescent cells after a single angioplasty, and larger numbers of senescent cells after repeated injury (fig. 4). These included both vascular smooth muscle cells and endothelial cells. In human pathology specimens, SA-β-gal positive endothelial cells have been demonstrated to overlay the atherosclerotic plaques in the aorta [28] and the coronary arteries [29], in contrast to the internal mammary arteries [29]. Taken together, these data implicate cellular senescence in the initiation and/or progression of atherosclerosis, and support the concept that the number of vascular cell replications that have taken place in the vessel wall increases not only as a function of chronological age, but also as a function of the haemodynamic or biochemical stress to the vascular bed. This would link vascular cell senescence to the "response to injury" hypothesis of atherosclerosis [30].

A role for telomere length in age-related vascular pathologies

Replicative senescence in its original form is triggered by the critical shortening of telomeres (fig. 2 and 3E, F). Therefore, comparing telomere length in tissue specimens should shed light on the replicative history of the cells contained therein, making telomere length a

Figure 4

Identification of senescent cells *in vivo* following carotid artery injury. Photomicrographs showing SA-β-gal staining in representative carotid artery cross-sections from rabbits having undergone sham (A, D), single (B, E) and double (C, F) denudations. D, E and F show high-power micrographs of areas close to the vessel lumen within A, B and C, respectively. The arrow in panel E indicates a single positively stained cell in the neointima of a single denudation vessel. Scale bars = 160 µm (A, B, C) and 20 µm (D, E, F). Reproduced with permission of the publisher.
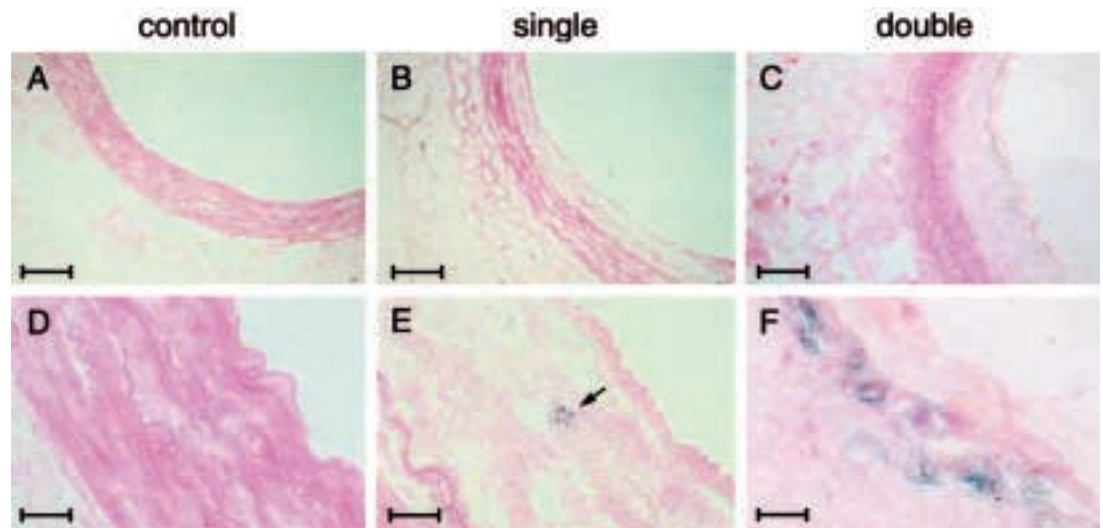
legitimate marker of senescence. In one of the first papers looking into a possible role for endothelial senescence in the aetiology of atherosclerosis, Chang and Harley found that the telomere length of intimal cells collected from post-mortems was significantly shorter in the iliac arteries than in the iliac veins [31]. Furthermore, the telomere length in the intima of the iliac artery was shorter than in the internal thoracic artery of the same donor, and this difference increased with advancing age of the donor. In contrast, cells from the media of these arteries had similar telomere lengths [31]. This inverse relationship between chronological age and telomere length in the endothelium was subsequently confirmed in tissues sampled from the human aorta [32, 33]. A recent paper examined the relationship between telomere length and coronary artery disease (CAD). The authors demonstrated that the telomeres in the coronary endothelium from autopsy specimens of patients with CAD were shorter than in age-matched specimens from donors without CAD [34]. Taken together, these papers support the hypothesis that focal replicative senescence and telomere shortening of the endothelium contribute to the age-related development of atherosclerosis.

Telomerase

The ribonucleoprotein telomerase is one the components of the telomere superstructure, and it plays a key role in the control of telomere length and cellular replicative capacity. Telomerase is a specialized reverse transcriptase that adds the sequence TTAGGG to the 3' ends of nuclear DNA [35]. Its two main components are a catalytic protein subunit known

as "human telomerase reverse transcriptase" (hTERT) and an RNA template (human telomerase RNA, hTR). This enzyme enables cells undergoing sustained proliferation to escape senescence by maintaining telomere length and chromosomal integrity despite repeated cell divisions. However, in most human somatic cells telomerase activity is down-regulated to a very low level. In post-natal life, substantial telomerase activity can be detected in germ line cells, which obviously must maintain their original telomere length and "youthfulness" through endless cell divisions [36], and in the stem cells of some normal somatic tissues that undergo sustained proliferative renewal, such as haematopoietic lineages and the epidermis [37]. Telomerase has become well known among medical professionals due to its infamous role in the development of cancer: maintenance of telomere length through vast numbers of cell divisions is one of the barriers that normal cells need to transcend in their path to malignant transformation. In about 85% of human malignancies, this is achieved by the loss of transcriptional control over telomerase and its pathological up-regulation [38], while the remaining 15% use a recombinatorial strategy of telomere maintenance known as "alternative lengthening of telomeres" (ALT) [39].

Telomerase activity in the vasculature

In the vasculature, telomerase activity can be detected in cultured vascular smooth muscle cells [40] and endothelial cells [41–43], although the level of activity found in proliferating endothelial cells is about 40-fold lower

than that of a typical human cancer cell line [43]. In human somatic cells, telomerase activity is tightly regulated at multiple levels, primarily by factors related to the proliferative status of the cell. Thus, in growth-arrested endothelial cells in culture, as well as in the intact endothelium in vivo, telomerase activity is down-regulated to a very low level [43]. Similar findings have also been reported for vascular smooth muscle cells [44]. A number of stimuli have been shown to induce or restore this activity in endothelial cells, including nitric oxide [42] and basic fibroblast growth factor (bFGF), a potent angiogenic growth factor [43]. Both transcriptional regulation of hTERT [43], post-transcriptional phosphorylation by the protein kinase Akt [45], and active transport of hTERT to and from the telomere [46, 47] have been implicated in the regulation of its activity. Genetic manipulation of human endothelial and vascular smooth muscle cells forcing them to overexpress hTERT enabled these cultures to escape senescence and dramatically extend their life span [40, 48]. Together with the original reports of this gene transfer experiment in human fibroblasts [49, 50], these findings have been of critical importance in supporting the telomere hypothesis of cellular senescence. It is important to emphasize that endothelial cells telomerised in this fashion are not malignantly transformed and display a normal cell culture phenotype [48]. Furthermore, telomerised endothelial cells create capillaries in vivo at least as efficiently as their primary parental cells, indicating that high levels of telomerase activity are able to maintain a youthful microvascular phenotype [51].

On the other hand, increasing evidence now indicates that telomerase plays a more complex role in the control of the cell cycle, involving functions beyond telomere maintenance. Inhibition of telomerase in vascular cells rapidly impairs their proliferative capacity in a manner which is independent of telomere shortening [43, 44]. Thus, endothelial cell cultures stimulated to grow with vascular endothelial growth factor (VEGF), which in the absence of bFGF does not restore telomerase activity, undergo senescence after only 10 population doublings, about a quarter of the life span achieved by cultures growing under bFGF stimulation [52]. These findings are in agreement with work in other cell types [53], showing that telomerase activity is essential to the upkeep of cellular proliferation in human somatic cells. This concept has important implications with regard to potential toxic ef-

fects of telomerase-inhibiting drugs. Clinical trials to assess the value of such compounds as anticancer agents are currently being planned, and potential strategies include long-term maintenance therapy of patients in clinical remission. In view of the newly discovered physiological role of telomerase in somatic cells, one might imagine a number of vascular side effects resulting from such therapies, including atherothrombotic events after loss of endothelial integrity or loss of atherosclerotic plaque stability and impaired formation of collaterals to ischaemic tissues [53, 54].

Do ageing mechanisms act in synergy?

The progressive oxidative damage of macromolecules resulting from the continual exposure of cellular components to oxidative stress is a process that has long been implicated in ageing and age-related pathologies [6]. It has become known as the "free radical theory of ageing". Interestingly, a large body of evidence now indicates that oxidative stress can also induce or accelerate the onset of replicative senescence [55]. This phenomenon has been collectively termed "stress-induced premature senescence" [56]. Earlier studies, primarily in fibroblasts, demonstrated that culture conditions with a high level of oxidative stress rapidly induced growth arrest and a senescent cellular phenotype, which was not associated with telomere loss [56]. However, other experiments using milder and more physiologically-ranged oxidative stress were found to induce premature senescence which could be attributed to accelerated telomere erosion [57], most likely resulting from the generation of single strand breaks in the telomeric DNA. More recently, evidence has been accumulating that oxidative stress can also accelerate the loss of telomere integrity and the onset of senescence in endothelial cells [58–60]. These effects have been induced by a variety of oxidant stressors, including homocysteine [58], pharmacological inhibition of endogenous antioxidant defence [59], and genetic manipulation inducing the activation of mitochondrial NAD(P)H-oxidase by *rac*1 [60]. An additional effect observed in endothelial cells even during mild oxidative stress was a rapid down-regulation of telomerase activity [59]. This was in agreement with other work, showing that oxidant substances with known pro-atherogenic properties such as oxidized LDL or tumour necrosis factor α also reduced telomerase activity in endothelial

cells [45]. Completing this picture of synergistic inter-dependency of ageing mechanisms, the metabolism of senescent cells seems to produce increased levels of reactive oxygen species [61]. In summary, these findings show that the ageing mechanisms of replicative senescence and oxidative stress promote each other, suggesting that they might contribute both to the ageing process in general and the development of age-related cardiovascular pathologies in a synergistic fashion (fig. 5).

### Is telomere length a hereditary determinant of age-related cardiovascular disease?

Telomere lengths in humans of the same age vary widely, with this variability being found at a number of levels. First, individual telomere lengths of different chromosomes within the same cell are very heterogeneous *(inter-chromosomal heterogeneity of telomere length)*. However, the pattern of chromosomal telomere heterogeneity is consistent between cells of the same species [62]. At the next level, mean telomere length varies between different cells of the same tissue, reflecting differences in the replicative history (degree of clonal expansion) of each cell *(inter-cellular heterogeneity of telomere length)*. Finally, mean telomere length varies considerably between individuals of the same age, both in neonates and in adults *(inter-individual heterogeneity of telomere length)*. Genetic studies performed in twins have demonstrated that these inter-individual differences in mean telomere length found in peripheral white blood cells (WBC) are to a large extent genetically determined, with 78% of inter-individual heterogeneity being due to hereditability [63]. Recent evidence suggests that the inheritance of telomere-length is X-linked, and therefore not conferred from fathers to their sons [64]. Apart from age, additional factors which have been shown to be associated with shorter WBC telomere length include male sex, smoking and high pulse pressure [64, 65].

It is known from human cells that both the replicative capacity (ex vivo) and the telomere length of these cells declines with increasing age of the donor [66]. Does this mean that individuals with shorter telomeres have a reduced capacity to regenerate their tissues in response to life long wear and tear? Observational studies seem to support this concept. In patients with severe coronary disease, WBC telomere length was shown to be shorter than age-matched controls [67]. The same researchers also found a significant association between shorter WBC telomere length and the risk of premature (<50 years of age) myocardial infarction [68]. Similarly, carotid atherosclerosis has been associated with shorter telomeres, when hypertensive patients with and without carotid artery plaques were compared [69]. Looking beyond atherosclerosis, we have recently demonstrated that patients with degenerative calcific aortic valve stenosis, an archetypal age-related disorder, have shorter WBC telomeres than controls matched for age, sex, and the presence or absence of coronary disease [70]. Shorter telomeres have also been associated with vascular dementia [71]. Until now, only one study has been able to examine the prognostic relevance of telomere length in a longitudinal fashion. In this study of 143 healthy individuals >60 years of age, shorter telomeres in WBC were associated with a 3.2

Figure 5

Synergistic contributions of ageing mechanisms to endothelial cell senescence. Endothelial cell renewal in response to chronic oxidative (and other) injury as well as oxidative stress in itself both contribute to telomere shortening and loss of telomere integrity. Oxidative stress can further induce a senescent phenotype independently of telomere damage, probably by activating DNA damage cell cycle checkpoints (stress-induced premature senescence). Downstream effector pathways are most likely independent of the initial stimulus. Finally, senescent cells have increased production of reactive oxygen species (red arrow).
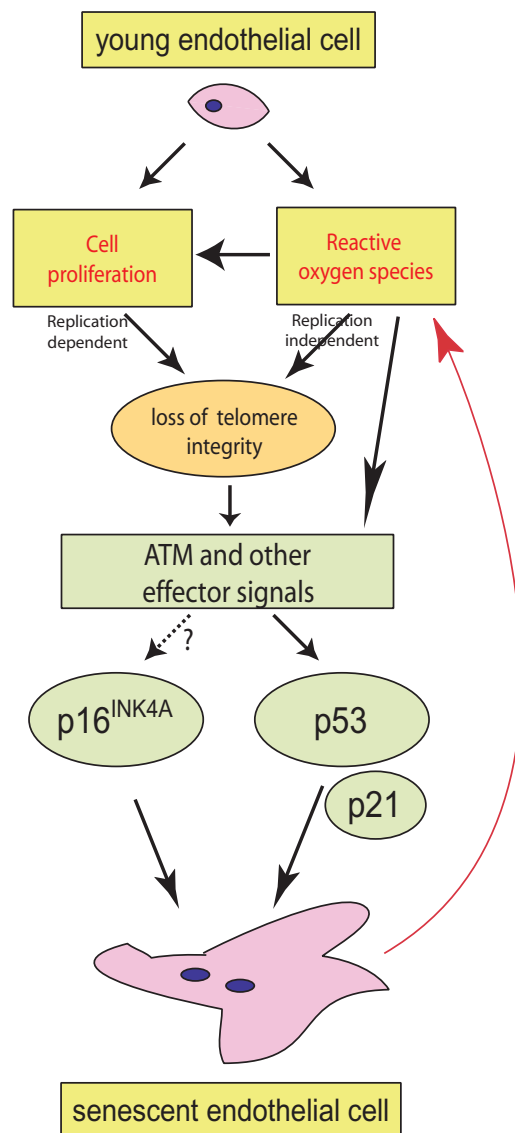
fold higher mortality rate from cardiovascular disease [72].

The results of studies investigating the association of telomere length in peripheral WBCs with cardiovascular disease states and/or its' risk factors are summarised in Table 1. Although these data appear to delineate a consistent line of evidence, it needs to be emphasized that these studies show only an association, without actually demonstrating that telomere shortening is a primary abnormality rendering organisms more susceptible to atherosclerosic risk factors. It has been argued that the shorter WBC telomere length found in atherosclerotic vascular disease might instead reflect the life-long increased turnover of WBCs associated with the chronic systemic inflammatory state in this disease [73]. According to this hypothesis, for which further evidence is equally lacking, shorter WBC telomeres in age-related vascular disease would be a secondary epiphenomenon without any causal involvement.

Evidence from human genetic mutations

A number of inherited disorders in humans are associated with a phenotype displaying features of premuture ageing. Patients with Werner syndrome, a rare autosomal recessive disease caused by mutations in the *wrn* gene (encoding a DNA helicase involved in DNA damage-repair), suffer from ageing of the skin, cataracts, diabetes and severe premature atherosclerosis in young adulthood [74]. These patients have an average life expectancy of 40–50 years. Telomeres in patients with Werner syndrome are normal at birth, but get shorter much quicker than usual. Progeria Hutchinson-Gilford is an extremely rare disease, in which children of kindergarten age have a wizened old appearance and usually die of coronary disease by the age of 10. The defect involves the gene Lamin A *(lmna)*, although it remains unclear how this results in the phenotype. These children are born with telomeres which are only about half as long as age-matched controls [75].

In contrast, two other well characterised inherited disorders associated with short telomeres and features of premature ageing, dyskeratosis congenita and ataxia teleangiectasia, do not feature accelerated development of atherosclerosis. Two different genetic variants of dyskeratosis congenita exist. The x-linked form has a mutation in the dyskerin gene, which is involved in ribosomal DNA processing and telomerase function, while the autosomal dominant form has a defect in the gene for the telomerase RNA component. Dyskeratosis congenita patients have reduced telomerase activity and short telomeres, and usually die in young adulthood of bone marrow failure, cancer or pulmonary complications [76]. Patients with the autosomal recessive disorder ataxia teleangiectasia have mutations in the *atm (ataxia teleangiectasia mutated)* gene, which encodes a protein involved in DNA damage repair. They suffer from neurological degeneration, premature ageing and increased neoplasia. Cells from these patients display accelerated telomere shortening in vitro, probably due to dysfunctional repair of oxidative damage to telomeric (and other) DNA [77]. The absence of atherosclerosis in patients with either of these disorders has been used to

Table 1
Conditions or diseases associated with short telomere length in peripheral white blood cells.

Condition / disease	n (patients)	age (mean or range)	control population	p-value	author	ref.
Cardiovascular mortality	143	>60	N/A (supra- *vs* submedian groups)	0.008	Cawthon	[72]
Coronary atherosclerosis	10	42–72	normal coronary arteries (n = 20)	0.002	Samani	[67]
Premature myocardial infarction (<50 years)	203	47 *vs* 47	healthy controls (n = 180)	<0.0001	Brouilette	[68]
Vascular dementia	41	18–98	healthy controls (n = 73)	<0.001	von Zglinicki	[71]
Hypertensives with carotid atherosclerosis	73	60 *vs* 64	hypertensives with no carotid atherosclerosis (n = 90)	0.03	Benetos	[69]
Age-related calcific aortic stenosis	30	77 *vs* 77	no aortic stenosis (n = 30)	0.002	Kurz	[70]
Increased pulse pressure	98	18–44	N/A (correlation)	0.0032	Jeanclos	[65]
Smokers	82	15–80	non-smokers (n = 189)	0.014	Nawrot	[64]
Men	119	15–80	females (n = 152)	0.028	Nawrot	[64]

argue against a role for telomere-based cell senescence in atherogenesis.

Cellular senescence and organismal ageing

The concept that telomere-based senescence may be a main player in the actual ageing process of multicellular organisms remains highly controversial. However, a role for this process in age-related degenerative disorders in humans, who as a species now outlive their evolution-driving life span by decades, seems more likely. An evolutionary ageing theory known as "antagonistic pleiotropy" suggests that genes or processes that were selected to benefit the health and fitness of young organisms can have unselected deleterious effects that are manifest in older organisms and thereby contribute to ageing. According to this, telomere-based replicative senescence might have been selected as a protective mechanism against the development of cancer during the years of reproductive activity. The downside of this protection is the onset of a senescence-driven loss of regenerative capacity, resulting in degenerative disorders at advanced ages at which natural selection will have no impact [78]. Another example of a cellular mechanism which protects against cancer, but promotes ageing, was recently described in a mouse over-expressing p53, an important tumour suppressing protein [79]. While these mice were resistant to cancer development, they displayed an accelerated ageing phenotype, illustrating the multi-faceted interaction between the senescence process and protection from cancer.

Concluding remarks

An increasing body of evidence now implicates telomere dysfunction and replicative senescence in the pathobiology of age-related cardiovascular disease. Both genetic and environmental factors influence telomere length, which display impressive inter-individual heterogeneity. Although shorter telomeres seem to be associated with a number of age-related cardiovascular disorders, their causal involvement remains unproven. The identification of telomere length as an element of inherited cardiovascular risk will have to await the outcome of prospective longitudinal studies.

Finally, therapeutic strategies targeting telomere length may be feasible, but long-term therapy will always need to be balanced against the risk of giving up the protection offered by the mitotic counter of senescence against the development of cancer.

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