

Review Article

Hallmarks of telomeres in ageing research

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Abstract

Telomeres are repetitive DNA sequences at the ends of linear chromosomes. Telomerase, a cellular reverse transcriptase, helps maintain telomere length in human stem cells, reproductive cells and cancer cells by adding TTAGGG repeats onto the telomeres. However, most normal human cells do not express telomerase and thus each time a cell divides some telomeric sequences are lost. When telomeres in a subset of cells become short (unprotected), cells enter an irreversible growth arrest state called replicative senescence. Cells in senescence produce a different constellation of proteins compared to normal quiescent cells. This may lead to a change in the homeostatic environment in a tissue-specific manner. In most instances cells become senescent before they can become cancerous; thus, the initial growth arrest induced by short telomeres may be thought of as a potent anti-cancer protection mechanism. When cells can be adequately cultured until they reach telomere-based replicative senescence, introduction of the telomerase catalytic protein component (hTERT) into telomerase-silent cells is sufficient to restore telomerase activity and extend cellular lifespan. Cells with introduced telomerase are not cancer cells, since they have not accumulated the other changes needed to become cancerous. This indicates that telomerase-induced telomere length manipulations may have utility for tissue engineering and for dissecting the molecular mechanisms underlying genetic diseases, including cancer.

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For every complex problem, there is a solution that is simple, neat, and wrong. [H L Mencken]

Introduction

Ageing is complex and there are a multitude of theories that attempt to describe organismal ageing in terms of simple/neat solutions that are almost guaranteed to be partially or totally wrong. While the telomere theory of ageing cannot explain all the complexities of organismal ageing, the following perspective reviews some of the recent observations hinting at telomere decline being involved in at least some aspects of human ageing. In addition, the use of telomerase for cell and tissue engineering offers a glimpse for a future of this area of research in regenerative medicine.

Ageing is associated with the gradual decline in the performance of organ systems, resulting in the loss of reserve capacity, leading to an increased chance of death [1]. In some organ systems, this loss of reserve capacity with increasing age can be attributed to the loss of cell function [2]. Chronic localized stress to specific tissues/cell types may result in increased cell turnover, focal areas of replicative senescence [3] followed by alterations in patterns of gene expression

[4,5]. This can result in reduced tissue regeneration, culminating in some of the clinical pathologies that are often associated with increased age.

Genetics is clearly important in determining cellular ageing *in vitro* and *in vivo* and part of organismal ageing may be dependent on cell division, with total cellular lifespan measured by the number of cell divisions (ie generations), not necessarily by chronological time [3,6]. This means that there is an intrinsic process occurring during cell growth which culminates in the cessation of cell division. If cellular age is regulated by a genetically determined counting programme that controls the number of cell divisions, then it is important to determine and understand the molecular pathways and regulation of this mechanism [7]. During the past 15 years, there has been mounting evidence that the progressive loss of the telomeric ends of chromosomes is an important intrinsic timing mechanism in the ageing process, both in cell culture and *in vivo* [8–10]. It is thought that the loss of telomeres eventually induces antiproliferative signals that result in cellular senescence [11–13]. While cellular senescence may have evolved initially as an anti-tumour protection mechanism, a hypothesis gaining prominence is that with increased population ageing, the activation of telomerase (a special ribonucleoprotein reverse

transcriptase important in maintaining telomere length stability) is a robust pathway that is engaged to bypass senescence and is required for the sustained growth of most tumours [14,15].

Setting the number of doublings

The amount of energy devoted to the maintenance and repair processes that keep our bodies healthy can be understood from theories of the evolution of ageing. The *disposable soma theory* [16] postulates that if more energy is invested in the repair of the soma (body), less is left for reproduction, while if too much energy is devoted to procreation, little is left for somatic repair. The balance between energy devoted to reproduction versus somatic repair may be the key to the rate at which species age. Species that have a high rate of annual mortality (and thus are unlikely to survive very long anyway) must invest most of their energy in early reproduction and relatively little in somatic maintenance and repair. A mouse that repaired itself sufficiently to live for 20 years would be making a bad investment, since most mice get eaten by foxes and owls within 3 months. The mouse is better off investing more energy in early reproduction and less in maintenance and repair. Humans, whose average survival is much longer than a mouse, would be selected for devoting much more energy towards tissue maintenance and repair than mice. A whole variety of maintenance and repair processes, such as the efficiency of DNA repair, protection against oxidative damage, the rate of protein turnover and the efficiency of the immune system, likely contribute to the genetic component of ageing. It is important in this context to recognize that limits in the amount of energy devoted to many different maintenance and repair processes are contributing to ageing, and that the role of replicative ageing discussed below would be only one (and perhaps a minor one) of a large variety of ageing mechanisms.

An efficient way of keeping cells healthy is triggering programmed cell death (apoptosis) of damaged cells and replacing them with new healthy ones. Replacing a dying cell with a freshly divided one also dilutes the build-up of 'unrepairable and undigestible' products that could contribute to ageing. However, using cell turnover to repair tissues carries risks as well as benefits. Mistakes in copying the DNA during cell division can lead to harmful mutations, so more divisions can lead to a greater risk of cancer. On the other hand, limiting the number of divisions provides an independent way of preventing malignancy (but may promote chronic diseases and ageing). In most cases it takes at least four to six mutations, if not more, to form a cancer cell [17]. Each mutation occurs in a single cell, which has to expand to at least a million cells before there is a reasonable probability for a rare additional mutation to occur. Furthermore, most cancer mutations are recessive. This means that once the

original mutant cell expands to a million cells, one of those cells needs to eliminate the remaining wild-type normal copy. This daughter then needs to expand again to a million cells to form a sufficient population size to permit additional mutations to occur. It takes 20 divisions for one cell to generate a million cells, so each cancer mutation probably uses up 20–40 divisions. Limiting the total number of times a cell could divide to less than 100 would thus prevent premalignant cells with one or two mutations from being able to divide and accumulate additional mutations. This would then form a powerful protection mechanism limiting cancer formation [18].

Human cells count the number of times they divide, and cultured human fibroblasts are able to divide only 50–80 times. This process of limiting cell divisions is called replicative ageing. Even though it is believed that the primary reason for counting and limiting the number of cell divisions is to form a barrier against the formation of cancer, these limits are likely to contribute to the physiology of ageing for the following reason. Very few of our Stone Age ancestors lived beyond 30–40 years of age, largely due to mortality from infections. Evolution would have sought a balance between the advantages of cell turnover for maintaining healthy tissues and the advantages of limiting the total number of times a cell divided to prevent cancer. One has to have a rate of cell division that is sufficient to keep us relatively fit during the reproductive years, but one should not have an enormous reservoir of unused cell divisions. As long as the probability of surviving beyond age 40 was historically very small, having sufficient cell divisions to allow us to be fit until age 120 would have carried an increased risk of cancer without any benefit. The number of permitted cell divisions would represent the balance between reducing the number as much as possible to increase the effectiveness as a brake against cancer formation, while permitting enough divisions for adequate maintenance and repair until about age 40. Modern sanitation, antibiotics, vaccines and other disease prevention interventions, as well as better treatment of established diseases, have now resulted in most of us living well beyond age 40. We believe that the restrictions on cell turnover imposed by replicative ageing, which would have little effect on physiology before age 40, are now contributing to part of the decline in tissue function that we call ageing as we grow older.

Senescence

The term 'senescence' has been used to primarily describe a signal transduction pathway leading to the phenomenon of irreversible growth arrest of cells in culture, accompanied by a distinct set of cellular phenotypic changes. There are a variety of mechanisms that can trigger cessation of cell proliferation (Figure 1) and all may be part of potent anti-carcinogenic programmes. In addition to senescence

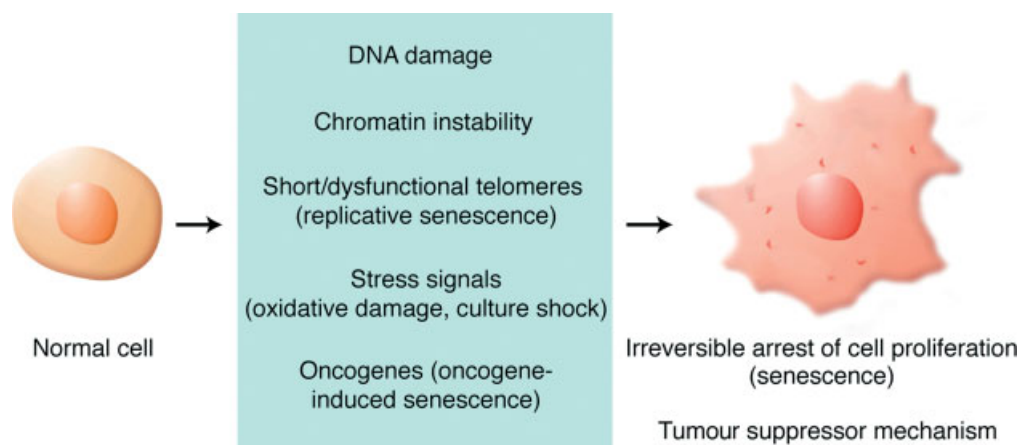


Figure 1. Mechanisms of senescence. In addition to progressive telomere shortening leading to irreversible growth arrest, other pathways include, DNA damage, chromatin instability, overexpression of oncoproteins, and a variety of stress signals (including oxidative damage). While morphologically the cells appear similar (greatly enlarge size), only replicative senescence shows shortened telomeres. The other mechanisms occurs with normal length telomeres. However, all of these mechanisms may be potent tumor suppressor pathway, initially limiting the growth of potentially malignant cells

being initiated by the shortening of telomeres, other endogenous and exogenous acute and chronic stress signals can also lead to irreversible cell cycle arrest, including oxidative damage, overexpression of oncoproteins, chromatin changes and DNA damage. The process of neoplastic transformation involves a series of events that allow cells to bypass or overcome these senescence pathways. The reader is referred to recent reviews on non-telomere-based initiators of senescence [19,20]. However, the focus of this perspective will be on what we term 'replicative' or 'telomere-based' senescence, which we have now learned is caused by a DNA damage signal initiated by the 'uncapping' of critically shortened telomeres [11]. When telomeres are unprotected by telomere-binding proteins, they are recognized as single- and double-strand DNA breaks and in normal cells there are no repair pathways; thus, cells senesce and can remain viable for years.

Telomeres

Vertebrate telomeres are repetitive, non-coding DNA (TTAGGG) elements at the ends of chromosomes that are capped with a series of single- and double-strand DNA binding proteins [21]. Telomeres shorten with each cell division due to incomplete lagging strand synthesis, less well understood end processing events and perhaps oxidative damage [22]. The shortening of telomeres occurs in rapidly proliferating cells of the skin, gastrointestinal system and blood. There are many correlative studies demonstrating a link between telomere length and ageing and there is a heritable component to telomere length [23,24]. In newborn humans, telomeres are approximately 15–20 kb in length and shorten gradually throughout life, suggesting that telomere length may serve as a biological counter, ticking off the passage of time with each cell division and providing a measure of

the replicative history of a cell. There is mounting evidence that once a critical shortened telomere length is attained, cell senescence is triggered. It is believed, but has not been proved, that when a subset of cells in a tissue reach a critically shortened telomere length, the senescent cells may produce a different constellation of proteins compared to those that are non-senescent but quiescent adjacent cells. When cells become senescent in a tissue, this could change the homeostasis of that tissue, leading to what most recognize as ageing.

These observations have led to a vast array of epidemiological studies in which telomere lengths have been measured in different tissues to analyse cellular replicative age. For example, a number of recent reports examining telomere length in peripheral blood mononuclear cells have reported correlations between shortened telomeres and a wide variety of age-related diseases, such as early myocardial infarction, vascular dementia, atherosclerosis and Alzheimer's disease [25–30]. Shortened telomeres from cells in affected tissues have been reported in patients with liver cirrhosis, Barrett's oesophagus, ulcerative colitis and myeloproliferative disorders [31–35]. Other precancerous lesions, such as ductal carcinoma *in situ* for breast cancer, and prostatic and cervical intraepithelial neoplasias, have been shown to have critically shortened telomeres *in situ* [31]. A correlation between shortened peripheral blood mononuclear cells and increased risk of death has even been found in subgroups of patients [36]. But do these studies prove that telomeres cause ageing or is it just a correlation? Also, do these short telomeres promote development of advanced disease or do the shortened telomeres and subsequent senescence actually act as potent anti-cancer protection mechanisms?

There is considerable inter-individual variability in telomere length, thus adequate sample sizes are critical in making firm cause-and-effect conclusions [37–50].

There are issues of survivor bias, as well as environmental factors, such as inflammatory disease and chronic infections, that could lead to misinterpretation of results. Importantly, the various techniques for measuring telomere length may not be reliable or reproducible within small ranges. Thus, measurements of telomere lengths in peripheral blood mononuclear cells are at best correlative and the utility of measuring telomeres as a surrogate for increased risk for age-related morbidity, or for predicting risk for the development of disease that have been reported in the literature, may in some instances be misleading [51]. It is important to re-emphasize that there is significant variability of telomere length within the cells and tissues of an individual and among groups of otherwise similar individuals, based on health status. Because there is a large amount overlap in the range of telomere length in the control and disease groups studied, the numbers of patients required to make meaningful interpretations is very high, in the hundreds if not thousands of patients, and few published studies have achieved these large datasets. Given the absence of a 'normal' telomere range for a given chronological age, it is difficult to imagine the utility of a single measurement of telomere length in an individual for prognostic purposes. Nevertheless, measurements of telomere length and studies of the mechanisms of telomere shortening may offer some insights into mechanisms of ageing [51].

Telomerase

Telomere length is maintained by a balance between processes that lengthen telomeres, such as the activity of the cellular ribonucleoprotein enzyme complex termed telomerase, and processes that shorten telomeres, such as a lack of complete lagging DNA strand synthesis and still poorly understood end processing events [8,21,52]. Telomerase stabilizes telomere length by adding TTAGGG repeats onto the telomeric ends of the chromosomes, thus compensating for the continued erosion of telomeres that occurs in its absence [53–55]. Telomerase contains two essential components [55–57], a telomerase reverse transcriptase catalytic subunit (TERT) [56] and a functional telomerase RNA (TR or TERC) [57]. Telomerase is expressed in embryonic cells and in adult male germline cells, but is undetectable in normal somatic cells except for proliferative cells of renewal tissues [58]. In all normal somatic cells, even those with detectable telomerase activity, progressive telomere shortening is observed, eventually leading to greatly shortened telomeres and to a limited replicative capacity [7,8]. Introduction of hTERT into telomerase-silent cells is sufficient to reactivate telomerase, elongate or maintain telomeres, and result in the bypass of both M1 senescence and M2 crisis [59,60]. Thus, telomeres are the molecular clock that counts the number of times a cell has

divided, and telomeres determine when cellular senescence [M1] and crisis [M2] occurs [61,62]. Several human diseases of telomere dysfunction have been discovered [63–71], and individuals born with reduced levels of telomerase have short telomeres. This leads to telomere dysfunction in highly proliferative cells, such as the bone marrow, resulting in diseases such as aplastic anaemia and, in some instances (likely in combination with additional genetic and epigenetic changes), increased risk for the development of leukemia [63–71]. This suggests that a more detailed knowledge of telomerase and telomere function may provide insights into human diseases.

Species that do not use replicative ageing

Mouse telomeres are extremely long in comparison to human telomeres, so that the shortest mouse telomere is longer than the longest human telomere. Mouse cells stop dividing after 10–15 doublings in culture, and 'spontaneously immortalize' so readily that it was initially debated whether or not they exhibited senescence. In contrast, the frequency of spontaneous immortalization in human fibroblasts in cell culture is essentially zero, and even after blocking the activity of RB and p53 with SV40 large T antigen, the frequency is only 10^{-7} [71]. This suggests that there might be fundamental differences between what was being described as 'senescence' in mouse fibroblasts and replicative ageing in human fibroblasts.

When the telomerase template RNA (mTR) was knocked out to eliminate telomerase activity, mice survived for many generations. Their telomeres became progressively shorter in successive generations, as expected. Importantly, the senescence that occurred in culture after 10–15 doublings in mouse embryo fibroblasts happened at the same number of doublings, regardless of whether first- or third-generation mice were used, and was thus independent of the initial telomere length [72]. This growth arrest thus could not be replicative ageing, since it was not caused by progressive replication-dependent telomere shortening.

Tissue oxygen concentrations are normally approximately 1–6% [73], so that the 21% oxygen of the typical sea-level culture room actually represents a hyperoxic environment. The hypothesis that the senescence of mouse embryo fibroblasts represented a general DNA damage response from oxidative damage was confirmed when it was shown that they showed no evidence of senescence if grown in low oxygen [74]. Thus, there is no evidence for replicative ageing in mouse cells obtained from inbred strains, since the only senescence seen is the growth arrest due to other causes.

The study of the mTR knockout mice showed that telomerase was not needed for mouse tumour formation [72]. This is in marked contrast to the behaviour of human tumours, where many studies have shown that the ongoing proliferation of most

human cancer cells (which usually have very short telomeres) is dependent on telomerase being able to maintain telomere length [75]. The concept that replicative ageing is an anti-cancer mechanism is based on progressive telomere shortening limiting the number of available cells divisions during which oncogenic mutations could accumulate. The normal frequency of tumour formation in mTR^{-/-} mice implies that replicative ageing is not used as an anti-cancer mechanism in mice, consistent with the size of their telomeres being so large that progressive shortening could not be used to count cell divisions in one generation.

Replicative ageing has been shown to be used in humans, primates [76] and sheep [77] and is thus not unique to humans. The presence of extremely long telomeres and the failure to exhibit replicative ageing is not restricted to inbred laboratory mice, but is also present in rabbits [78] and many other wild species (unpublished results). A working hypothesis to explain this in the larger context of ageing is that there may be trade-offs between the advantages of having short telomeres/using replicative ageing as an anti-cancer mechanism and having very long telomeres/not using replicative ageing, so that different evolutionary choices can be made.

One possible, but as yet unproved, source of this trade-off might be the amount of energy invested in protecting telomeres from oxidative damage. Oxidative intermediates can travel along the DNA and preferentially produce damage at triplet GGG sequences [79,80]. Not only are telomeres thus more sensitive to oxidative damage, but DNA damage at telomeres is repaired less efficiently, due to the fundamental nature of telomeric proteins hiding telomeres from being recognized as damaged DNA needing repair [81,82]. Species occupying a niche in which their annual mortality is so high that they are over-investing in oxidative protection mechanisms (as a general repair/longevity assurance mechanism) would be selected to reduce that investment. One consequence of this would be increased telomeric damage and the production of cells with a rapid growth arrest due to one or a few severely shortened telomeres. If the annual mortality of this species was sufficiently high that they very rarely developed cancer, it might thus be advantageous to compensate by abandoning the anti-cancer benefits of short telomeres and replicative ageing in favour of extremely long telomeres that could tolerate greater levels of oxidative breakage, as well as not suppressing telomerase in most tissues during development, so that broken telomeres could be elongated rather than stimulating a growth arrest. In fact, telomerase expression is found in several adult mouse tissues (eg liver) in which it is suppressed in humans. Given that some species age perfectly well without appearing to use replicative ageing, it is important not to overemphasize the role of replicative ageing in overall ageing but to focus on areas in which human ageing may differ from ageing in the mouse [83].

Is the presence of telomerase a molecular determinant of preneoplasia and early cancer detection?

The diagnosis of cancer is generally made by a pathologist who examines a tissue sample for characteristic morphological abnormalities. Because pathologists must primarily rely on subtle cellular alterations, diagnostic pathology in some instances is not always an exact science. While progress has been made towards developing more accurate nucleic acid-based tests to assess tissue specimens, most of these methods do not have sufficient specificity (ie ability to differentiate between normal, precancerous and cancerous cells) and sensitivity (accuracy in detecting the presence of cancer) to identify a wide variety of cancer types. Therefore, new clinical assays applicable to most types of cancer are needed.

We and others have been examining the potential of telomerase, an enzyme whose expression is elevated in most human cancers (Table 1), to be used as a sensitive biomarker for screening, early cancer detection, prognosis, or in monitoring as an indication of residual disease. The detection of telomerase activity has been evaluated using commercially available research assays on fresh or fresh frozen tumour biopsies, fluids and secretions. During the past 5 years there have been hundreds of manuscripts published on the topic of telomerase and cancer (for reviews, see [75,84]). With few exceptions, these have shown that reactivation or up-regulation of telomerase activity and its template RNA (hTR) and catalytic protein component (hTERT) are associated with a higher percentage of all cancer types investigated (Table 2). Detection of lesions prior to the onset of tissue invasion is one important goal of telomerase screening, but the development of clinical telomerase diagnostics will require additional validation studies and standardization methodologies [85–87].

Table 1. Telomerase activity in cleared margins, preinvasive and malignant cancers

Pathology	Positive/ tested (n)	Positive (range) (%)
Normal tissue or adjacent to malignancy	367/2350	15.5 (0–100)
Preinvasive cancer	410/1391	29.5 (0–67)
Malignant	3615/4304	84.0 (8–100)

Table 2. Telomerase expression in major cancer sites

System or site	Annual deaths (1998)	Telomerase positivity
Respiratory	165 600	431/541 (80%)
Digestive	130 300	1136/1330 (85%)
Reproductive	66 900	709/801 (89%)
Haematological	59 200	117/157 (75%)
Breast	43 900	777/896 (87%)
Urinary	24 700	392/443 (89%)

Anti-telomerase cancer therapy

Current cancer therapy regimens for patients with advanced cancer generally include tumour resection followed by intensive chemotherapy and/or radiation therapy. Since telomerase activity is detected in almost all advanced tumours, the use of telomerase inhibitors may provide an effective and novel approach to cancer therapy. Normal somatic cells that lack telomerase expression should be largely unaffected by anti-telomerase therapy. Anti-telomerase therapies may be most effective when used in conjunction with surgical tumour reduction, and perhaps in combination with, or followed by, conventional chemotherapies and/or radiation. Telomerase inhibitors may be most effective in reducing the risk of relapse by targeting cancer stem cells and the small numbers of telomerase-positive cancer cells in adjacent tissues not removed during tumour resection [88–91]. Telomerase inhibitors should lead to progressive telomere shortening in the cancer cells and result in growth arrest and/or cellular senescence. Since most normal somatic cells do not express telomerase, this type of agent may also possess greater specificity, lower toxicity and reduced side-effects.

The primary unwanted effect of telomerase inhibition therapy might be on telomerase-positive reproductive cells and other proliferative cells of renewal tissues [88–91]. Cells from such tissues generally have much longer telomeres than most tumour cell populations. Anti-telomerase treatment for tumours could be designed to finish before telomere depletion in these cell types. Because the most primitive stem cell populations only rarely divide, their telomeres should shorten at a much slower rate than telomerase-inhibited, proliferating cancer cells. Furthermore, stem cells of renewal tissues may be less affected than dividing tumour cells; they proliferate only transiently, and telomerase activity is negligible in the absence of cell division. For solid tumours, there is no evidence that a subset of stem-like cells remain quiescent for long periods of time. After the cancer cells have shortened their telomeres and stopped proliferating and/or died, anti-telomerase therapy could

be discontinued, and telomerase activity in reproductive and stem cells would be restored. Thus, anti-telomerase therapy is predicted to eliminate the proliferative potential of cancer cells before the telomere lengths in normal reproductive and stem cells shorten sufficiently to disrupt their function. There have been several recent studies in this area of research [92–94].

Numerous telomerase inhibitor strategies have been developed that are in the preclinical or other stages of clinical trials (Table 3). These have been reviewed in detail recently [94]. Perhaps one of the most rapidly advancing areas of telomerase therapy involves immunotherapy or vaccines targeting telomerase. Telomerase may be processed differently in cancers and it has been determined that human hTERT-specific epitopes are expressed on cancer cells but not on normal cells. Clinical trials involving patients with lung, breast, prostate and pancreatic cancers have been conducted, with excellent and encouraging results [95–97]. No patients have had treatment related side-effects (such as autoimmune disease or bone marrow stem cell depression). Thus, late-stage clinical trials are now being initiated and, if the preliminary results hold up in randomized trials, FDA approval may be forthcoming.

Telomerase therapy for age-associated disease

There is a Dr Jekel and Mr Hyde aspect to telomerase. Importantly, telomerase is not causative but permissive for advanced tumour cell growth. In contrast, telomerase is expressed at high level in the male germ line and in embryonic stem cells. We and others have shown that the expression of the catalytic subunit of human telomerase (hTERT) reconstitutes telomerase activity and circumvents the induction of senescence [98–104]. We have used hTERT to extend the lifespan of a variety of human cell types, including skin keratinocytes, dermal fibroblasts, muscle satellite (stem) cells, endothelial cells, retinal-pigmented epithelial cells, breast epithelial cells, and both corneal fibroblasts (keratocytes) and corneal

Table 3. Telomerase targets and related therapies

Strategic target	Expected outcome of intervention at target	Who is working on the target	Therapies in trial
hTERT vaccine (TVAX)	Cancer remission/prevention of relapse	Robert Vonderheide, University of Pennsylvania Medical (www.med.upenn.edu) Geron Corporation (www.geron.com) & Johannes Vieweg, Duke University Medical Center (www.mc.duke.edu) Gustav Gaudernack, Norwegian Radium Hospital (www.radium.no)	Yes Yes Yes
hTR/hTERC oligonucleotide	Telomerase enzyme inhibitor, telomere shortening	Geron Corporation (http://www.geron.com/)	Yes
hTERT oncolytic virus	Killing of telomerase-positive cells	Cell Genesys (www.cellgenesys.com)	No

TVAX, tumour vaccine; hTERT, human telomerase reverse transcriptase; hTR/hTERC, human telomerase RNA.

Conclusions

Telomerase activity is detected in the vast majority of human cancers. Detection of telomerase may help pathologists to diagnose and risk-stratify a variety of cancers more effectively. The bottleneck at present is that additional validation studies and clinical trials will be required before knowledge of telomerase activity will be useful in a practical sense for decisions regarding patient management.

A key area to pursue is determining the particular types of cancer that exhibit clinically useful correlations between telomerase activity and either diagnostic or prognostic outcomes. Molecular staging using markers such as telomerase activity, most likely in combination with other molecular markers, may have great promise to help in this regard. Finally, the utility of inhibitors of telomerase in the therapy of cancer should be revealed in the next few years.

There is mounting evidence that cellular senescence acts as a 'cancer brake' because it takes many divisions to accumulate all the changes needed to become a cancer cell. In addition to the accumulation of several mutations in oncogenes and tumour suppressor genes, almost all cancer cells are immortal and, thus, have overcome the normal cellular signals that prevent continued division. Young normal cells can divide many times, but these cells are not cancer cells, since they have not accumulated all the other changes needed to make a cell malignant. In most instances cells become senescent before they can become cancer cells. Therefore, ageing and cancer are two ends of the same spectrum. Inhibition of telomerase in cancer cells may be a viable target for anti-cancer therapeutics, while expression of telomerase in normal cells may extend healthy lifespan. This may be particularly important in specific age-related diseases in which increased cell turnover due to the pathological process results in replicative senescence and a failure to maintain physiological function. In summary, telomerase and its regulation of telomere length is an important target for both cancer and the treatment of age-related disease. The telomerase gene will likely have many important applications in the future of medicine and cellular engineering.

Additional information

Additional information can be obtained at the following website: <http://www4.utsouthwestern.edu/cellbio/shay-wright/>

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