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## Telomerase and the aging process

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### Abstract

The level of telomerase activity is important in determining telomere length in aging cells and tissues. Here evidence on the importance of telomerase activity is reviewed with respect to aging rates of mammalian species and the health and life span of individuals within a species. The significance of telomerase reactivation for both cancer development and for immortalizing cells for therapeutic processes is assessed.

### Keywords

Telomerase; telomeres; senescence; cancer; immortalization

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Telomeres are the specialized repetitive DNA sequences at the ends of the linear chromosomes, and associated proteins, that serve to maintain the integrity of the chromosomes. Telomerase is a ribonucleoprotein DNA polymerase complex that maintains telomere length. The complex comprises the protein telomerase reverse transcriptase (TERT, or hTERT in humans) and a catalytic RNA (TERC) (Shay and Wright, 2007). In the absence of telomerase activity telomeres progressively shorten. Telomerase activity is absent in most normal human somatic cells because of the lack of expression of TERT; TERC is usually present. On the other hand most mouse cells have telomerase activity (Blasco, 2005). Without telomerase, telomere shortening eventually limits the growth of cells, either by senescence, in cells with intact cell cycle checkpoints (a G1 cell cycle block), or by crisis in cells with inactivated checkpoints (telomeric end-to-end fusions cause chromosome breakage and mitotic catastrophe) (Shay and Wright, 2007). Expression of TERT in cells that otherwise lack telomerase activity causes cells to bypass senescence and crisis, and such cells are usually termed “immortalized.” The significance of senescence, crisis and immortalization is explored further in this review (see Figure 1).

### 1. Do telomere biology and telomerase activity determine aging?

The first aspect to this question is whether differences in aging rates among mammalian species are caused in whole or in part by species-specific differences in telomerase/telomere biology. A very brief consideration of this question will show that this is unlikely. Mice are short-lived compared to humans, yet mice have long telomeres and adult mouse somatic cells often have telomerase activity (Blasco, 2005). On the other hand, humans have relatively short telomeres, even when compared to closely related primates (Kakuo et al., 1999), and telomerase activity

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is very low in most cells, except for some types of stem cells, the germ line, and some somatic cells such as T lymphocytes (Shay and Wright, 2007). If telomere exhaustion were a major cause of aging one would expect humans to be relatively susceptible to this process and mice to be resistant; obviously the much longer life span of humans would suggest that differences in telomere biology is not a major determinant of life span among mammals. However, this simple argument leaves open two related questions: first, are differences in telomere biology important determinants of aging and life span among individuals within a species; and second, even if telomerase and longevity are not positively correlated, is it possible that they could be negatively correlated: could high telomerase activity be a factor causing shorter life span?

The question of whether differences in telomere biology are important determinants of aging and life span among individuals within a species is only meaningful in species such as humans that have limited telomerase activity. Nevertheless, it is possible to address the question of the consequences of shortened telomeres in tissues by engineering mice to lack telomerase activity. Mice with defects in the *TERC* gene undergo generation-dependent telomere shortening. In later generation telomerase-deficient mice various organs exhibit impaired functions, demonstrating that sufficiently short telomeres do have an adverse impact on tissue function (Blasco, 2005). However, experiments in mice cannot answer the question of whether telomeres ever reach a “critical” length, i.e. a length that impairs proliferation (or conceivably some other cellular property), in any tissue in humans during a normal life span. There is little evidence that commonly observed changes in older individuals, such as anemia and impaired wound healing, result from impaired cellular proliferation, which would be the anticipated consequence of shortened telomeres (Hornsby, 2001). Despite the lack of clear evidence for impaired proliferation in aging there is, in fact, good evidence for progressive telomere shortening in many human cell types, including peripheral white blood cells, smooth muscle cells, endothelial cells, lens epithelial cells, muscle satellite cells, and adrenocortical cells, among others (Hornsby, 2001). One example is of particular interest: proliferative capacity is closely related to telomere length in endothelial cells. Telomere lengths in endothelial cells decreased as a function of donor age, with a greater decline being observed in cells isolated from the iliac artery in comparison to cells from the thoracic artery (Chang and Harley, 1995). The greater decline in telomere length was observed in the cells had likely undergone more proliferation *in vivo*, because they resided in a part of the vascular system where blood flow might cause most chronic damage to the endothelium. However, it is difficult to test this hypothesis directly.

Thus telomere shortening does indeed occur in the human body during aging. The question, as stated above, is whether this telomere shortening is a determinant of differences in aging and life span among individuals. Two aspects to this question are: (i) whether telomere length, as measured in specific cell populations in the body, correlates with longevity or disease; and (ii) whether telomere shortening in any cell population causes *functional impairment* of that cell population. At the present time the only cell populations that have been subjected to the required depth of analysis are peripheral white blood cells and some white blood cell subsets.

Several observational studies have attempted to gain insight into the question of whether age-related telomere shortening in human peripheral white blood cells is associated with health and disease status. One study concluded that “in and of itself, SES [socioeconomic status] appears to have an impact on WBC [white blood cell] telomere dynamics” (Cherkas et al., 2006). Another study of mothers of chronically ill children concluded that “psychological stress is associated with indicators of accelerated cellular aging [including] telomere length” (Epel et al., 2004). Both of those studies suggest an influence of perceived psychological status on telomere length. Of course, psychological stress does not necessarily cause stress at the cellular/molecular level. One plausible link is the endocrine system (Cohen et al., 2006). Possibly the explanation for the differences in telomere length in individuals of differing psychological

status lies in the actions of hormones such as glucocorticoids on cell death and cell proliferation in the hematopoietic system.

Some clinical procedures may turn out to be inadvertent experiments that address the issue of whether short telomeres in peripheral white blood cells causes functional impairment. In recipients of bone marrow transplants the hematopoietic system can suffer a dramatic telomere shortening, perhaps the equivalent to several decades of “aging” (Wynn et al., 1998). Some data suggest that long-term survivors of bone marrow transplants may suffer immune dysfunction as a consequence of the combination of the sudden loss of telomere length at the time of transplantation followed by normal age-related shortening (Lewis et al., 2004).

This area of research, i.e. epidemiological correlations between white blood cell telomere length and longevity or disease is a complex topic and a general review such as this one cannot do it justice; the topic has been the subject of an excellent recent review in this journal (Baird, 2006). One aspect should be mentioned, and that is that overall changes in telomere length could be the result of changes in subsets of cells. In this context it is of interest that expansion of blood CD8<sup>+</sup> T lymphocytes is associated with all-cause mortality (Wikby et al., 2002; Pawelec et al., 2005). CD8<sup>+</sup>CD28<sup>-</sup> T lymphocytes have telomeres that are shorter than those of other white blood cells from the same individual (Monteiro et al., 1996; Effros et al., 1996); this may be connected to the observation that loss of CD28 expression is also associated with loss of ability of T lymphocytes to upregulate telomerase activity (Valenzuela and Effros, 2002).

It must be remembered that no observational studies, whether on the entire white blood cell population or on subsets, can establish cause and effect. Such studies cannot be interpreted as indicating that shorter telomeres in some individuals (e.g. those with a higher level of psychological stress) have an adverse effect on health or mortality. In the case of both total white blood cells and T lymphocyte subsets there may be excessive cell proliferation, as a result of various causes, which then leads telomere shortening. Perhaps, short telomeres may be only an age-associated but benign or inconsequential marker, like graying of the hair or senile lentigenes of the skin. These age-related changes do result from profound alterations in melanocytes, including melanocyte stem cells (Nishimura et al., 2005), but do not cause age-related morbidity or mortality.

There are at least three major questions that need to be answered. First, we need to know what telomere length in human tissues is associated with *functional impairment*, of specific organs, tissues or cell populations; second, because of the great heterogeneity in telomere lengths between cells and between different telomeres within cells, we need to know if there could be impairment of individual of cells, even if there is no measurable deficit in the cell population as a whole; and third, we do not know if telomere length in white blood cells, or T lymphocytes, correlates with telomere length in other tissues. Gaining access to appropriate tissue samples to test this is problematic. Is there a specific cell population in the body in which telomere length *directly determines* differences in health, disease or the actual rate of aging among individual humans? This is possible, but we have no evidence to support the existence of such a population of cells.

## 2. Telomeres, telomerase and tumor suppression

The second major question posed at the beginning of this review is whether high telomerase activity could be a factor causing shorter life span. In fact there is evidence that short telomeres and a lack of telomerase can exert a longevity-promoting effect via prevention of cancer. Of course, this does not mean that short telomeres/lack of telomerase cause a slower rate of aging. Instead it is reasonable to hypothesize that any species which has evolved a slower rate of aging will also need to evolve mechanisms for reducing susceptibility to premature death from cancer.

The short telomere/lack of telomerase combination acts as a tumor suppressor mechanism in mammals, as detailed below.

Telomere shortening eventually leads to cellular senescence, a permanent form of growth arrest (Shay and Wright, 2007). The number of times normal cells can divide before senescence is a constant for a particular cell population growing under a specific set of culture conditions, thus giving rise to the idea of a mitotic clock.

In the early development of the field, the processes of senescence and telomere shortening were closely linked and were often discussed as a single phenomenon. Subsequently it became evident that telomere shortening was only one of many ways in which cells could become senescent. A non-telomere-based mechanism, oncogene-induced senescence, represents one of two mechanisms by which senescence exerts an anti-cancer effect (Figure 2). The complex topic of oncogene-induced senescence has been reviewed elsewhere (Mooi and Peeper, 2006). The second mechanism is probably *not* the operation of telomere shortening in an otherwise normal cell, as is often assumed --instead it is probably the operation of telomere shortening in a progressively abnormal cell clone, as illustrated in Figure 2. The reasoning for this assertion is this: if a cell clone is normal, without oncogene activation, then by definition reaching a state of critically short telomeres, at which point the cell stops dividing, does not prevent a cancer. If oncogene-activated or DNA damage-dependent senescence occurs, then also by definition it is not telomere shortening that acts to prevent cancer. On the other hand, it is very likely that in cells in which multiple oncogenic mutations have occurred the limitation on cell division imposed by shortened telomeres is a final way for the body to delete a potentially harmful clone of cells. This is a terminal state for the clone, unless it escapes by becoming immortal. A clone of cells that has avoided being eliminated by apoptosis, senescence or differentiation over many cell generations has likely acquired multiple mutations. Most fully developed cancer cells have a large number of mutations; human colorectal and breast cancers each have an average of ~90 mutant genes, of which a somewhat smaller number are required for the neoplastic properties of the cell (Sjoblom et al., 2006). Mutations in cell cycle checkpoint pathways such as p53 and pRb are common, thereby eliminating the senescence response to telomere dysfunction (Prescott and Blackburn, 1999).

Because such cells have undergone extreme telomere shortening they reach the state called "crisis." In this state, short dysfunctional telomeres cause end-to-end chromosome fusions; in cells with disrupted checkpoints this results in (i) breakage-fusion-bridge cycles, leading to increasing aneuploidy; and (ii) mitotic catastrophe, a failure of cytokinesis, resulting in tetraploidization, multipolar cell division, and gross aberrations in chromosome number (Maser and DePinho, 2002). Mitotic catastrophe leads to arrest in mitosis, or alternatively to the formation of cells with multiple nuclei or a single giant nucleus. Cells with abnormal nuclei and other features of mitotic catastrophe are often observed in human cancers (Gisselsson, 2003).

The evidence that crisis is a reliable barrier to continued growth of tumorigenic cells comes from experiments in which SV40 large T antigen and oncogenic Ras were expressed in normal human fibroblasts; these cells were transplanted beneath the kidney capsule of immunodeficient mice (Sun et al., 2005). Surprisingly, these two genes were sufficient to convert normal human cells into aggressively growing cancers that invaded the kidney and other organs and metastasized to the lungs. They were nevertheless not immortal, and tumors could not be serially transplanted. In all cases tumors entered crisis and no escapes via activation of telomerase or other mechanisms were observed in more than 200 animals that received transplants of these cells (Sun et al., 2005; and unpublished observations). The lack of escape by immortalization indicates that crisis reliably prevented the continued growth of the cancer.

An obvious question, in light of these experimental results, is why telomerase-negative cancers that have a history of self-limiting growth are not observed clinically. There may be a few cancers that do grow extensively and then stop because of lack of telomerase (Hiyama et al., 1995). Probably more frequently cancers that lack telomerase and do not acquire sufficient telomerase activity never grow large enough to be clinically detectable. The exception to that statement may be dermatological cancers, which have a greater likelihood of being detected at very early stages. Small squamous cell carcinomas may lack a telomere maintenance mechanism (Gordon et al., 2003). In a mouse, a 2-gram cancer that is not immortal can grow large enough to kill the animal (Sun et al., 2005). In a human a similarly sized cancer may well be clinically undetectable, and after the cells enter crisis and eventually die little trace of the neoplasm's existence may remain. Although cells in experimental tumors that enter crisis do not die by apoptosis they do eventually die via nonspecific necrosis that occurs after the tumor stops enlarging (Sun et al., 2005). As early detection of cancer improves, it may become more common to find very small malignant lesions that lack telomere maintenance mechanisms.

If, at some point during the growth of the clone or at crisis, cells within the clone acquire a sufficient level of telomerase activity for telomere maintenance then crisis can be bypassed (Maser and DePinho, 2002; Shay and Wright, 2007). Most cancer cells have activated mechanisms of telomere maintenance, mostly as a result of increased expression of TERT (Shay and Wright, 2007). Thus the lack of telomerase, or the lack of sufficient telomerase activity to permit immortal growth, exerts a significant barrier to the formation of a lethal cancer from a clone of cells that otherwise has a set of mutations that give it cancer properties.

In human cells the combination of short telomeres (i.e. short as a species) and suppression of TERT expression together provide an anti-cancer mechanism. The existence of this anti-cancer mechanism in humans but not in mice may be one factor contributing to the large difference in susceptibility to cancer, calculated on a per cell basis, between mice and humans (Hornsby, 2005). Yet the same combination of short telomeres and lack of TERT expression could limit the ability of tissues to respond to injury and stress in old age (Hornsby, 2001), although the evidence for and against this possibility is mostly lacking, as stated above. If this is correct, the anti-cancer process may provide an example of antagonistic pleiotropy, the genetic event (repression of TERT) having beneficial effects in early life span and possibly negative effects in late life span (Campisi, 2003).

### 3. The potential role of telomerase in cell therapy in aging

Beginning with the first reports of hTERT-immortalization, it was speculated that this technology could be used to expand populations of cells for subsequent therapeutic transplantation (Bodnar et al., 1998). This was thought of as particularly important for the replacement of tissues and organs damaged during aging (Shay and Wright, 2000). In one proposed form of this therapy, cells with shortened telomeres would be isolated from a patient and telomere length restored by hTERT expression. The cell population would be expanded in culture and then cells would be reintroduced into the body to restore tissue and organ function. In this scheme, hTERT plays a role in autotransplantation. hTERT-immortalization could also be useful in allotransplantation and xenotransplantation, by allowing expansion of cells with specific properties, such as stem cells or genetically modified cells.

As immortalization by hTERT became more widely studied, it became apparent that hTERT may exert effects on cells beyond extension of proliferative potential. In many cases hTERT-modified cells have widespread changes in gene expression, a topic discussed further below. The combination of immortalization and altered gene expression might make hTERT-immortalized cells particularly attractive for cell therapy and related technologies such as tissue engineering (Shay and Wright, 2000). A variety of hTERT-modified cells have been used in

experimental cell therapy (Ulaner, 2004). A notable recent example is the construction of blood vessels engineered with hTERT-expressing smooth muscle cells (Klinger et al., 2006). Distinguishing the mechanisms by which hTERT affects cell proliferation versus cell function will be important so that the desirable features of each may be separately controlled.

As described above, our studies on experimental cell transplantation of genetically modified cells show that hTERT does not cooperate with known oncoproteins in tumorigenesis. Only when telomeres have shortened to a critical level is telomerase activity needed for continued growth of the tumor. The question that should be considered is whether the latter conclusion would mean that hTERT modification could render cells more dangerous *in vivo* if they subsequently underwent mutational changes that caused activation of oncogenes. In all of the experiments we have performed using bovine and human adrenocortical cells, as well as human fibroblasts, we never observed sporadic formation of tumors from cells modified by hTERT alone. Therefore, we can begin to form an estimate of the upper limit to the rate of neoplastic conversion of hTERT-modified cells. Further studies are needed to define this limit and thereby to determine more accurately the risks of using hTERT-modified cells in cell therapy. However, the fact that hTERT does not cooperate with known oncoproteins shows that hTERT is not an oncogene.

TERT-expressing cells show extensive changes in gene expression patterns; the ability of hTERT to exert a variety of effects that counteract cell death is striking (Sung et al., 2005) and these effects have been reported also in whole animals overexpressing TERT; in mice this protects against experimental heart failure (Oh et al., 2001) and has many other effects in the cardiovascular system (Serrano and Andres, 2004). hTERT-expressing cells are more resistant to chromosome damage caused by ionizing radiation (Pirzio et al., 2004). The changes in gene expression in hTERT-modified cells enable them to survive and grow in sites in the body where otherwise they do not grow, such as the subcutaneous space, which is in essence a harsh site for even the most robust cells to survive in (Sun et al., 2005).

The wide range of gene expression changes does not give unequivocal pointers as to the important changes conferred by ectopic hTERT that lead to improved cell survival and growth. Further studies will be valuable in determining these changes and using the information to improve transplantation of normal cells in cell therapy. It would be desirable to use hTERT to provide only immortalization and to confer other desired properties by separate specific genetic modifications.

## Conclusions

Telomerase is probably not a factor in determining the differences in aging rate among species. Telomere shortening resulting from the absence of telomerase activity may be a factor in determining some age-related properties of organs in humans. Reactivation of telomerase could be useful in some forms of cell therapy and does not appear to present a problem with safety. However, activation of telomerase removes a barrier to the continued growth of developing cancers; lack of telomerase activity provides a tumor suppressor function.

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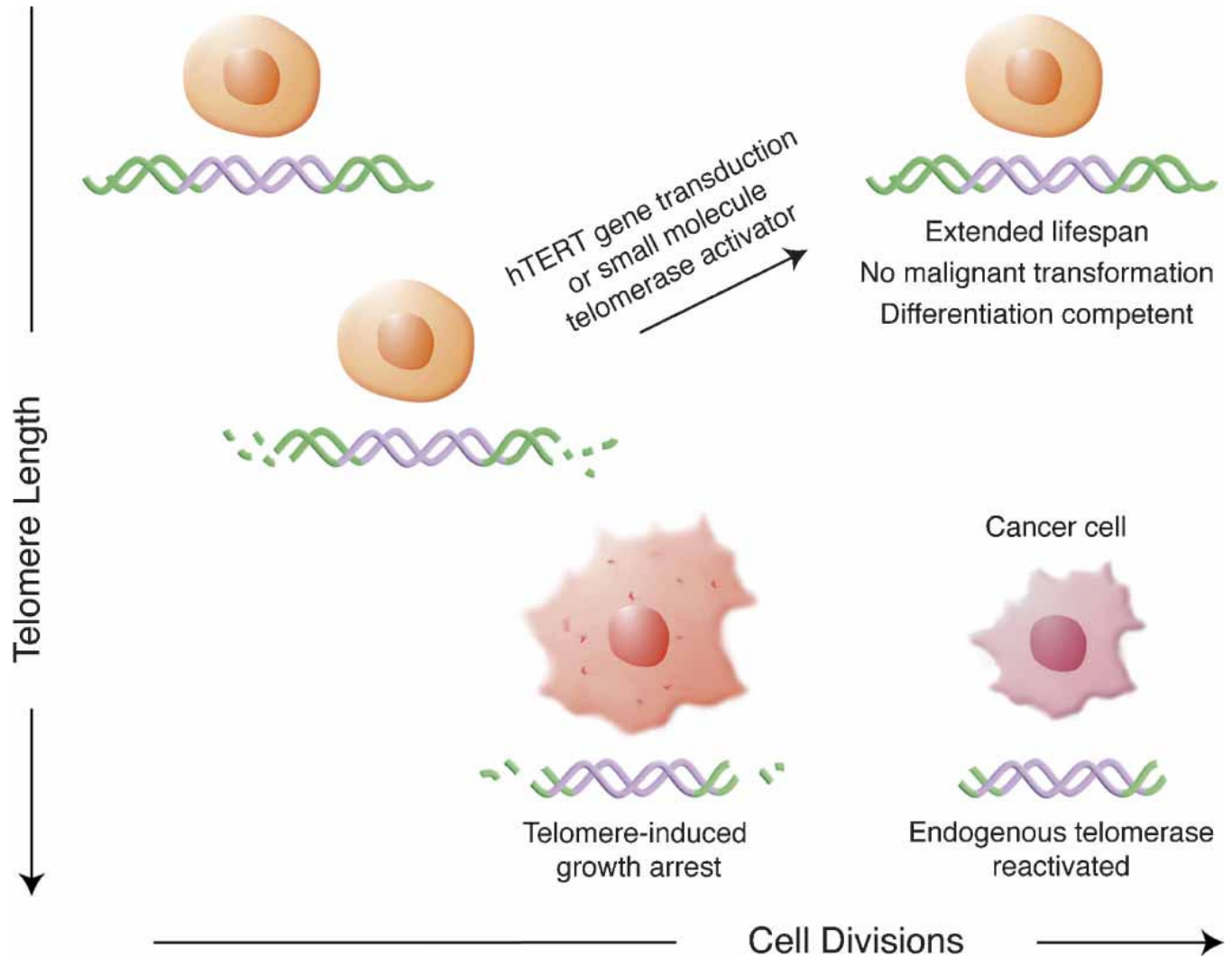
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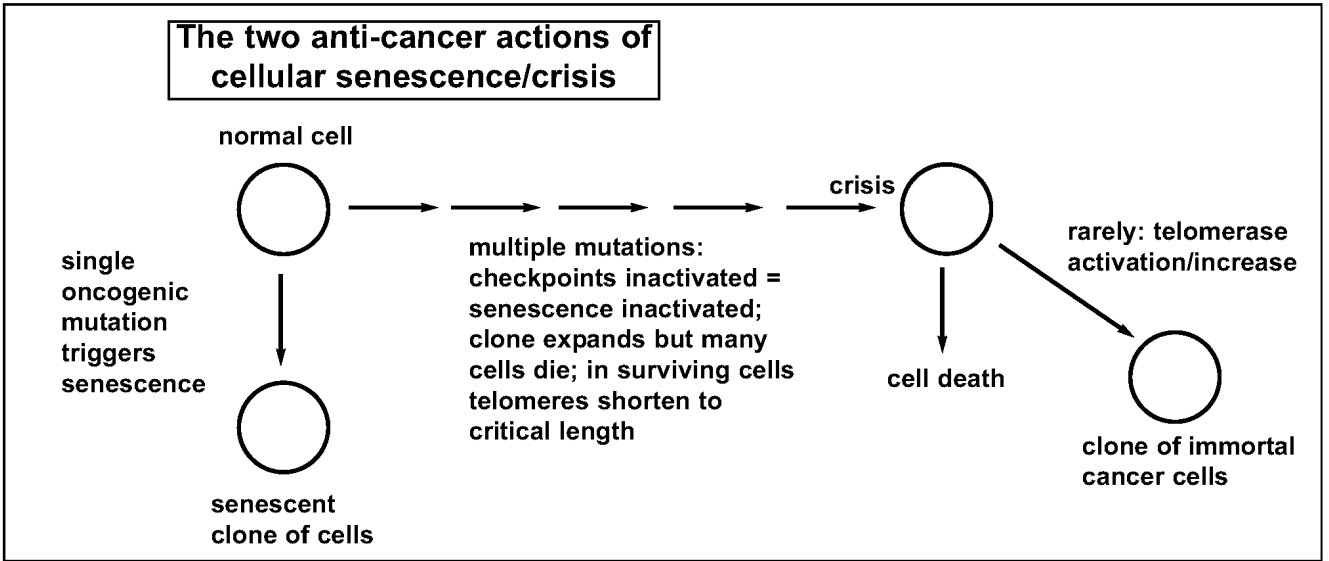
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**Figure 1.**

The absence of telomerase activity in most human somatic cells results in telomere shortening during aging. Telomerase activity can be restored to human cells by hTERT gene transduction or potentially via drug therapy; such extended-lifespan cells could be useful in forms of cell therapy to be developed for age-related diseases. On the other hand, the absence of telomerase acts as a limitation on cancer growth unless telomerase becomes reactivated. Reproduced with permission from Shay and Wright, 2007.



**Figure 2.**

The two anti-cancer mechanisms of cellular senescence. Left: Senescence can be triggered by an oncogenic mutation. The oncogenic protein both stimulates cell proliferation and triggers senescence, with the result that, despite some expansion of the clone, the cells eventually cease dividing. The end result is a benign lesion, such as a nevus. Right: When an abnormal cell clone acquires multiple mutations over time, one or more of the mutations act to inactivate cell cycle checkpoints. In this case the cell clone continues to divide; senescence is inactive and so cannot act to limit the proliferation of the cells. Many cells within the clone die or are lost as result of differentiation or immune surveillance. If cells in the clone continue to divide telomeres progressively shorten until they become so short as to cause end-to-end fusions. Breakage-fusion-bridge cycles may ensue. This state (crisis) is a terminal one for the cell and the cell will eventually die. However either before crisis or during crisis telomerase may be upregulated. In that case telomere erosion is stopped and an immortal cell clone arises. Because of the many mutations that the cell has acquired by this time the cell may already be tumorigenic or may have acquired many of the mutations needed to reach that stage.