



# Sowing the seeds of cancer: telomeres and age-associated tumorigenesis

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## Purpose of review

Advances in the health system and medical sciences are continuously pushing the barrier of life-expectancy. As a consequence, humans are being increasingly afflicted by age-associated diseases, such as cancer. The challenge now lies in understanding the mechanisms underlying ageing in order to reduce the lifetime risk for cancer.

## Recent findings

In long-lived mammals, telomere length and restriction of telomerase activity are important barriers preventing the uncontrolled cell division. Absence of telomerase dictates the continuous telomere erosion with each cell division, thus restraining the proliferation of incipient tumour cells. However, recent findings have revealed the unintended consequences of telomere control of cell division. Cells with short telomeres accumulate in older individuals increasing the risk of telomere depletion. Loss of telomere protection results in tetraploidization and genomic instability characteristic of epithelial cancers. Additionally, telomere shortening blocks cell proliferation and induces cell senescence. Senescent cells secrete proinflammatory factors and reactive oxygen species that increase the likelihood of cellular transformation and create the perfect soil for cancer development.

## Summary

Telomere shortening thus provides an example of antagonist pleiotropy, in which a beneficial characteristic that acts during the reproductive years of an organism may, later in life, contain the seed to its demise.

## Keywords

ageing, cancer, senescence, telomerase, telomeres

## INTRODUCTION

Cancer is primarily a disease of older people, with incidence rates increasing with age for most cancers. In the European Union, nearly nine out of 10 cancers are diagnosed in people aged 50 and over [1]. More than any other, age is the strongest risk factor for cancer. However, the mechanisms whereby age influences the susceptibility to develop cancer are far from being understood and the question remains: why does cancer incidence increase with age?

The current paradigm, the ‘mutation accumulation hypothesis’ proposed by Peter Medawar in 1952, predicts that mutations accumulate at a low frequency throughout the lifetime of an organism [2]. Thus, cancer would be the end result of a sequential accumulation of somatic mutations required to break down the physiological barriers protecting from tumorigenesis. In this view, age would simply reflect the time required for the appropriate combination of mutations to occur. However, this concept does not explain how cancer affects

organisms with so different lifespans and sizes (the so-called Peto’s paradox [3]). Given the conservation of mutation rate and DNA repair amongst mammals, one would expect a far higher incidence of cancer in animals that undergo more cell divisions [4,5]. Instead, cancer death rates vary only approximately two-fold across mammal species that span 1000-fold in mass and 100-fold in lifespan [6]. Thus, other protective mechanisms against cancer should exist that account for these fundamental differences.

In this review, we will discuss how telomerase restriction in somatic tissues and consequent telo-

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## KEY POINTS

- Telomere protection is an example of antagonistic pleiotropy, providing an explanation for the increased cancer incidence with age.
- During reproductive life, telomeres shorten in dividing cells preventing uncontrolled cell proliferation and limiting tumorigenesis.
- Later in life, senescent cells with short telomeres accumulate.
- Critically short telomeres induce tetraploidization and genomic instability, promoting carcinogenesis.
- Senescent cells provide an inflammatory microenvironment permissive for cancer progression.

mere shortening provides an independent and complementary explanation linking ageing with increased cancer risk. We propose that telomere shortening in long-lived mammals is an example of antagonistic pleiotropy, in which benefits collected during the early reproductive years provide the basis of detrimental effects later in life. Commonly accepted as important barriers to the development of cancer, telomere shortening and senescence have damaging consequences later in life, acting as both 'seed and soil' for the development of cancer in older individuals.

## SHORT TELOMERES CONSTITUTE A BARRIER TO CANCER

In humans and other long-lived mammals, telomere shortening and repression of telomerase represent important protective mechanisms against cancer development [7].

Telomeres are nucleoprotein complexes composed of (TTAGGG)<sub>n</sub> repeats and a specialized protein complex (known as shelterin) that protect chromosome-ends from being recognized as deleterious DNA double-strand breaks (DSBs) and activate DNA damage responses (DDR) [8,9]. Telomere length is maintained by telomerase, a specialized reverse transcriptase that adds TTAGGG repeats to the end of chromosomes. However, telomerase activity is repressed in most somatic tissues after embryogenesis [10], resulting in progressive telomere shortening with each cell division because of the 'end-replication problem' [8]. After a set number of cell divisions, telomeres inevitably become critically short losing the ability to protect chromosome-ends. Upon telomere depletion, chromosome-ends trigger DDRs culminating in cell-cycle arrest as a means to control cell proliferation.

Telomere dysfunction may also be triggered by oncogene activation and other insults, resulting in DDRs and cell-cycle arrest without telomere shortening [11<sup>22</sup>]. Telomeres constitute preferential sites for accumulation of DNA damage signalling molecules, perhaps because of the inability of repairing DNA lesions [12<sup>2</sup>,13<sup>2</sup>]. Thus, chromosome-ends may act as sinks of genotoxic stress capable of activating the senescence programme whenever their structure and function are compromised.

The evidence that cells have a finite replicative potential was first described by Hayflick in cultures of primary human fibroblasts [14]. Subsequent work by Greider and Harley demonstrated that telomere shortening represented the basis for the molecular clock that limited the proliferative capacity of cells [15]. These findings came together when Shay and Wright reintroduced telomerase in cultured primary human fibroblasts. By stabilizing telomere length, telomerase alone was sufficient to bypass senescence gaining unlimited cell proliferation [16]. Crucially, these cells maintained the characteristics of normal fibroblasts, thus acquiring immortalization without cancer features.

Thus, progressive telomere shortening functions as a cell-autonomous barrier against overproliferation, yielding a potent tumour-suppressor mechanism. However, maintaining telomeres short enough whilst using the full potential of replicative senescence results in unintended consequences, as we will discuss next.

## THE SEED: SHORT TELOMERES BREAK THE SENESCENCE BARRIER

Even though telomere shortening provides a tumour-suppressor mechanism, it may, paradoxically, be at the root of cancer in older individuals.

The spectrum of tumours that typically affects the elderly is dominated by the cancers of epithelial origin, which are often associated with marked genomic instability and karyotypic diversity [1,17]. Several lines of evidence suggest that telomere dysfunction is a common driver for genomic instability present in cancer [18]. Support for this idea was provided by Artandi and DePinho using late-generation, telomerase-deficient mice [19]. Laboratory mice, which have 5–10× longer telomeres than humans, are prone to develop lymphomas and sarcomas, a cancer profile typical of children. Instead, mice engineered to have short telomeres shift the tumour spectrum towards carcinomas carrying cytogenetic abnormalities, typical of cancers that affect older humans.

Oncogenic mutations, occurring as early as embryogenesis, provide cells with survival advantage

that allows them to overproliferate, leading to progressive telomere shortening [11<sup>■</sup>]. Dysfunctional telomeres may themselves promote mutagenesis. DDRs triggered by damaged chromosome-ends promote mitochondrial dysfunction and oxidative stress [20<sup>■</sup>,21]. Increased levels of reactive oxygen species (ROS) in cells can drive the acquisition of new mutations. When surveillance genes are mutated, such as the ones that lead to p53 inactivation, cells may overcome the senescence barrier and continue to divide, resulting in total loss of telomere function. Once telomeres become deprotected, chromosome-end fusions are often observed followed by successive breakage–fusion–bridge cycles [18]. Genomic instability generated by telomere loss (also known as Crisis) generally results in cell death and thus should still be considered a barrier to cell proliferation. However, the very few cells capable of surviving this period may have taken a big leap into carcinogenesis. Tetraploidization, non-reciprocal translocations and aneuploidies are all formed during this stage, increasing the probability of acquiring somatic mutations that promote cancer progression [22,23<sup>■</sup>].

One of the key events in tumorigenesis is the re-expression of telomerase. Counteracting genomic instability, telomerase expression reconstitutes telomere protection, ensuring chromosomal stability and provides cells with infinite replicative capacity [24,25]. Presence of telomerase in 90% of all human cancers reinforces the need to balance telomere attrition to maintain unlimited proliferation [26]. Recent studies confirm that reactivation of telomerase is important for cancer progression and acquisition of full malignant traits. Using an inducible mTERT transgene in a prostate cancer mouse model, Ding *et al.* [27<sup>■</sup>] manipulated telomerase expression so that reactivation would occur after the onset of telomere dysfunction. They observed that re-expression of telomerase in the prostate epithelium generated more aggressive tumours, driving metastatic progression. Genome analysis of these tumours revealed cytogenetic changes similar to the ones observed in human prostate cancers. These and other observations are reminders of the benefits that antitelomerase therapies are likely to have to combat cancer [28].

In this view, telomeres can offer only a time-dependent protection. Initially, telomere shortening may prevent cells from overproliferating. However, these cells inevitably accumulate with time and, by sheer increase in numbers, potentially dangerous clones eventually bypass the barriers that restrain them. Thus, the mechanisms that initially protect cells against cancer (telomere shortening and senescence) may, in time, give rise to new mutations and potential malignant traits.

## THE SOIL: SHORT TELOMERES PROMOTE A CANCER-PRONE MICROENVIRONMENT

Despite the benefits of telomere shortening as a cell-autonomous tumour-suppressor mechanism, the resulting accumulation of senescent cells with age may have deleterious effects on tissue homeostasis, ultimately providing a permissive environment to tumour progression.

Cellular senescence is a unique state of proliferative arrest, in which cells have ceased division but remain metabolically active and resistant to apoptosis [29]. Even though other stimuli are capable of triggering cell senescence [30], short telomeres are the inevitable consequence of cell proliferation in an organism that generally lacks telomerase. In contrast to apoptotic cells, senescent cells are not efficiently cleared from tissues. This results in an age-dependent accumulation of cells that continuously activate tissue repair mechanisms [31]. Permanent tissue damage signalling modifies the surrounding microenvironment and provides the appropriate cues for cancer development.

Senescent cells secrete a number of growth factors, proinflammatory cytokines and proteases generally designated as the senescence-associated secretory phenotype (SASP) [32]. SASP is triggered by persistent DDRs initiated by the markers of DNA damage preferentially located at telomeres [12<sup>■</sup>,13<sup>■</sup>,33<sup>■</sup>]. This secretory phenotype has autocrine and paracrine effects that may explain the different and antagonistic aspects of cellular senescence at the organism level. SASP factors contribute both to the stimulation of tissue repair [34] and to the maintenance of cell senescence [35] (local effects), but also to tissue dysfunction and inflammation (organismal effect) that contribute to ageing and age-related diseases [36].

A causal relation between senescent cells and age-related tissue dysfunction was recently established in the BubR1 progeric mouse model [37<sup>■</sup>]. Using this transgenic model with inducible elimination of p16<sup>Ink4a</sup>-positive cells, Baker *et al.* showed that clearance of senescent cells delayed the onset of age-related phenotypes in tissues such as muscle, eye and adipose tissue. Strikingly, elimination of these cells later in life could also halt the progression of pre-established ageing phenotypes. The authors suggested that the acquisition of SASP was the mechanism contributing to the age-related tissue dysfunction and inflammation.

The relationship between cancer and inflammation has long been established [38]. Increased cancer incidence with age may be instigated by SASP through a chronic inflammatory microenvironment. Initial studies by Campisi and colleagues revealed that factors secreted by the senescent cells

in tissue culture can have effects on cell differentiation and cell proliferation, induce epithelial-to-mesenchymal transition [39,40], and stimulate angiogenesis and cell migration [41]. Further evidence from in-vivo experiments using mouse xenograft models showed that senescent cells coinjected with malignant and premalignant epithelial cells promoted tumour growth and invasiveness [39,42]. Specific factors secreted by senescent cells, such as matrix metalloproteinases (MMPs), were responsible for the protumorigenic effect, disrupting tissue integrity giving rise to the perfect permissive 'soil' for malignant cells.

Thus, age-dependent accumulation of senescent cells induced by telomere shortening may, ultimately, be at the root of the chronic inflammatory environment and tissue remodelling long associated with the tumour development. This idea is supported by the clinical evidence in which conditions associated with increased cell proliferation and inflammation, such as ulcerative-colitis or liver cirrhosis, are characterized by telomere shortening and cancer predisposition [43].

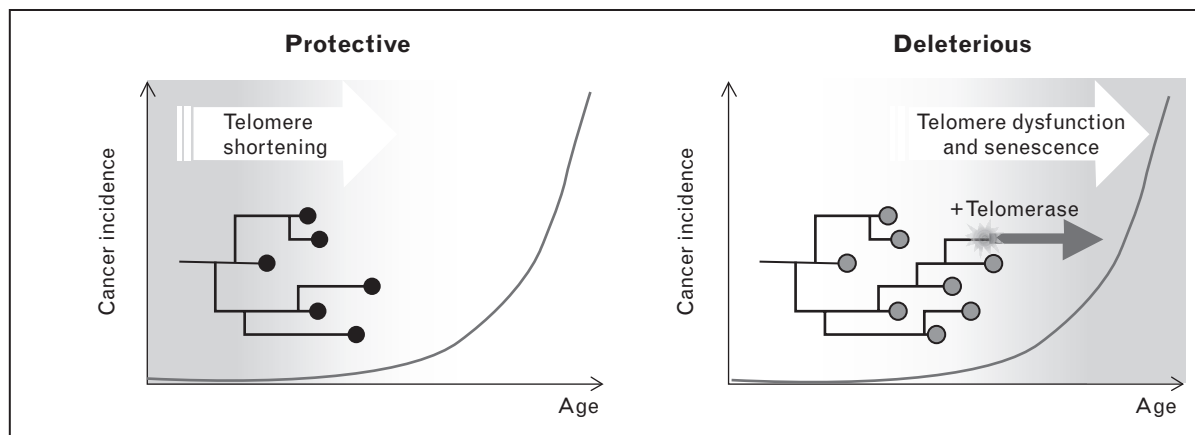
## CONCLUSION

Evolution of repressed telomerase activity and short telomeres in humans and other long-lived mammals represents an adaptive mechanism to limit cancer during reproductive age [7]. However, telomere depletion and replicative senescence produces unintended deleterious consequences in later nonreproductive life.

One such trade-off is the age-dependent accumulation of cells that have reached their replicative potential because of critical telomere shortening. Proliferation beyond this limit will drive further telomere erosion and increased chromosomal instability, raising the chance of acquiring novel mutations and cellular transformation. The increased number of cells poised in this premalignant state, statistically, makes it more probable for one of these cells to acquire the ability to reactivate telomerase (or alternative mechanisms of telomere elongation) and gain malignant potential (Fig. 1).

A second trade-off resulting from telomere shortening with age is the alteration in tissue microenvironment induced by senescent cells. These age-related changes in tissue milieu characterized by stromal abnormalities and smouldering inflammation favour the progression of incipient carcinogenesis to its full potential. Not only increased numbers of senescent cells relax the rules against hyperproliferation imposed by the tissue, but also contribute to general cell mutagenesis by generating ROS and inflammatory cytokines (Fig. 1).

In the current model, we propose telomere shortening to be the fundamental mechanism linking the different aspects of the ageing process and providing a framework to explain the increase of cancer after reproductive age. In an example of antagonist pleiotropy, telomere shortening provides protection from uncontrolled cell division during the reproductive years, but ultimately leads to an increased risk of cancer later in life.



**FIGURE 1.** Duplicitous roles played by telomeres in cancer and ageing. In long-lived mammals, telomeres play antagonistic roles in cancer development. Cancer incidence increases exponentially with age (red line). During reproductive years (left), telomere shortening functions as a barrier to hyperproliferation (black circles) limiting tumorigenesis. Throughout life (right), senescent cells with short telomeres increase in frequency (grey circles). As these cells accumulate in older individuals, few may escape and lose telomere protection. As a consequence, they undergo genomic instability acquiring mutations required for cancer progression and reactivation of telomerase (arrow). Senescent cells additionally secrete inflammatory factors and metalloproteinases that generate a protumorigenic microenvironment.



If telomere erosion were indeed responsible for the increase of cancer with age, would reversing this process prevent the development of cancer in later life? Telomerase-based therapies are being tested as means to mitigate telomere shortening and ameliorate ageing symptoms. Initial studies using stable transgenic mouse lines uncovered that the eventual benefits of telomerase expression were frustrated by an increase in cancer incidence, both induced and spontaneous [44,45]. More recently, however, studies by Blasco and colleagues suggest that the induction of telomerase in adult mice (either chemically induced or via adenovirus) would reduce age-related disorders and increase life-expectancy without higher incidence of cancer [46<sup>■</sup>,47<sup>■</sup>]. These apparently contradictory results may simply reflect the pressure of telomerase overcoming the tumour-suppressive mechanism in the transgenic models. It is possible that a therapeutic approach to telomerase, rather than constant expression, may have the benefit of reducing senescence cells whilst keeping telomerase generally restrained. Nevertheless, most studies have been conducted in mouse models with long telomeres that are not depleted during their short lifetime. In order to clarify this question, it will be important to conduct similar studies in animals that, like humans, use telomere shortening as a barrier to cell proliferation.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 102).

1. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer* 2012.
  2. Medawar P. An unsolved problem in biology. London: H.K. Lewis & Co.; 1952.
  3. Peto R, Roe FJ, Lee PN, *et al.* Cancer and ageing in mice and men. *Br J Cancer* 1975; 32:411–426.
  4. Lynch M. Evolution of the mutation rate. *Trends Genet* 2010; 26:345–352.
  5. DeGregori J. Evolved tumor suppression: why are we so good at not getting cancer? *Cancer Res* 2011; 71:3739–3744.
  6. Caulin AF, Maley CC. Peto's Paradox: evolution's prescription for cancer prevention. *Trends Ecol Evol* 2011; 26:175–182.
  7. Gomes NM, Ryder OA, Houck ML, *et al.* Comparative biology of mammalian telomeres: hypotheses on ancestral states and the roles of telomeres in longevity determination. *Aging Cell* 2011; 10:761–768.
  8. De Lange T. How telomeres solve the end-protection problem? *Science* 2009; 326:948–952.
  9. Carneiro T, Khair L, Reis CC, *et al.* Telomeres avoid end detection by severing the checkpoint signal transduction pathway. *Nature* 2010; 467:228–232.
  10. Forsyth NR, Wright WE, Shay JW. Telomerase and differentiation in multicellular organisms: turn it off, turn it on, and turn it off again. *Differentiation* 2002; 69:188–197.
  11. Suram A, Kaplunov J, Patel PL, *et al.* Oncogene-induced telomere dysfunction ■ enforces cellular senescence in human cancer precursor lesions. *EMBO J* 2012; 31:2839–2851.
- This study shows that oncogene-induced senescence is activated by DDR foci at dysfunctional telomeres independently of telomere length. It provides strong evidence that oncogene-induced senescence is an important tumour-suppressor mechanism in humans, preventing tumour growth at premalignant stages.
12. Fumagalli M, Rossiello F, Clerici M, *et al.* Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nat Cell Biol* 2012; 14:355–365.
- This study and the one below demonstrate that telomeres are the preferential sites of DNA replication stress and accumulation of DDR markers. In contrast to other chromosome sites, telomeric damage gives rise to persistent DDR signalling that induces cellular senescence. This study highlights the role of telomere as guardians of genotoxic stress.
13. Hewitt G, Jurk D, Marques FD, *et al.* Telomeres are favoured targets of a ■ persistent DNA damage response in ageing and stress-induced senescence. *Nat Commun* 2012; 3:708.
- See Ref. [12<sup>■</sup>].
14. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res* 1961; 25:585–621.
  15. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature* 1990; 345:458–460.
  16. Bodnar AG, Ouellette M, Frolkis M, *et al.* Extension of life-span by introduction of telomerase into normal human cells. *Science* 1998; 279:349–352.
  17. Edwards PA. Fusion genes and chromosome translocations in the common epithelial cancers. *J Pathol* 2010; 220:244–254.
  18. Murnane JP. Telomere dysfunction and chromosome instability. *Mutat Res* 2012; 730:28–36.
  19. Artandi SE, Chang S, Lee SL, *et al.* Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature* 2000; 406:641–645.
  20. Sahin E, Colla S, Liesa M, *et al.* Telomere dysfunction induces metabolic and ■ mitochondrial compromise. *Nature* 2011; 470:359–365.
- Telomere dysfunction impairs mitochondrial biogenesis and function through a p53-dependent repression of the PGC network. This mechanism may explain the age-related abnormalities occurring in postmitotic tissues, such as heart and liver.
21. Lawless C, Jurk D, Gillespie CS, *et al.* A stochastic step model of replicative senescence explains ROS production rate in ageing cell populations. *PLoS One* 2012; 7:e32117.
  22. Davoli T, Denchi EL, de Lange T. Persistent telomere damage induces bypass of mitosis and tetraploidy. *Cell* 2010; 141:81–93.
  23. Davoli T, de Lange T. Telomere-driven tetraploidization occurs in human cells ■ undergoing crisis and promotes transformation of mouse cells. *Cancer Cell* 2012; 21:765–776.
- This study provides evidence that telomere-driven tetraploidization occurs in human cells revealing the importance of telomere shortening for cancer. Tetraploidization occurs during Crisis and it has the potential to promote tumorigenesis.
24. Artandi SE, DePinho RA. Telomeres and telomerase in cancer. *Carcinogenesis* 2010; 31:9–18.
  25. Shay JW, Wright WE. Role of telomeres and telomerase in cancer. *Semin Cancer Biol* 2011; 21:349–353.
  26. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. *Eur J Cancer* 1997; 33:787–791.
  27. Ding Z, Wu CJ, Jaskeliouff M, *et al.* Telomerase reactivation following telomere ■ dysfunction yields murine prostate tumors with bone metastases. *Cell* 2012; 148:896–907.
- In this study, the authors provide evidence supporting the fundamental role of telomere dysfunction and telomerase reactivation in tumorigenesis. Re-expression of telomerase after telomere dysfunction in a prostate cancer-prone mouse model yields more aggressive tumours with enhanced metastatic potential, with aberrant chromosomal rearrangements typically found in human prostate cancer.
28. Buseman CM, Wright WE, Shay JW. Is telomerase a viable target in cancer? *Mutat Res* 2012; 730:90–97.
  29. Blagosklonny MV. Cell cycle arrest is not yet senescence, which is not just cell cycle arrest: terminology for TOR-driven aging. *Aging (Albany NY)* 2012; 4:159–165.
  30. Ogrunc M, d'Adda di Fagnola F. Never-ageing cellular senescence. *Eur J Cancer* 2011; 47:1616–1622.
  31. Jayapalan JC, Ferreira M, Sedivy JM, Herbig U. Accumulation of senescent cells in mitotic tissue of aging primates. *Mech Ageing Dev* 2007; 128:36–44.

32. Coppe JP, Patil CK, Rodier F, *et al.* Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* 2008; 6:2853–2868.
33. Rodier F, Munoz DP, Teachenor R, *et al.* DNA-SCARS: distinct nuclear structures that sustain damage-induced senescence growth arrest and inflammatory cytokine secretion. *J Cell Sci* 2011; 124:68–81.  
The authors define nuclear structures termed DNA-SCARS and explain how different DDRs are activated by persistent and transient foci. These results confirm that sustained DDR signalling is fundamental for the activation of the senescence programme and cytokine secretion that constitutes the SASP.
34. Jun JI, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat Cell Biol* 2010; 12:676–685.
35. Acosta JC, O'Loughlin A, Banito A, *et al.* Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell* 2008; 133:1006–1018.
36. Rodier F, Campisi J. Four faces of cellular senescence. *J Cell Biol* 2011; 192:547–556.
37. Baker DJ, Wijshake T, Tchkonia T, *et al.* Clearance of p16Ink4a-positive ■ senescent cells delays ageing-associated disorders. *Nature* 2011; 479:232–236.  
In this study, the authors provide evidence that senescent cells are causally implicated in the development of age-related disorders in a BubR1 progeroid mouse model. They show that removal of p16Ink4a-positive cells delays the onset of age-related phenotypes and attenuates the progression of already established ones.
38. Colotta F, Allavena P, Sica A, *et al.* Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009; 30:1073–1081.
39. Krtolica A, Parrinello S, Lockett S, *et al.* Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc Natl Acad Sci USA* 2001; 98:12072–12077.
40. Parrinello S, Coppe JP, Krtolica A, Campisi J. Stromal–epithelial interactions in aging and cancer: senescent fibroblasts alter epithelial cell differentiation. *J Cell Sci* 2005; 118:485–496.
41. Coppe JP, Kauser K, Campisi J, Beausejour CM. Secretion of vascular endothelial growth factor by primary human fibroblasts at senescence. *J Biol Chem* 2006; 281:29568–29574.
42. Liu D, Hornsby PJ. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. *Cancer Res* 2007; 67:3117–3126.
43. Risques RA, Lai LA, Himmetoglu C, *et al.* Ulcerative colitis-associated colorectal cancer arises in a field of short telomeres, senescence, and inflammation. *Cancer Res* 2011; 71:1669–1679.
44. Gonzalez-Suarez E, Samper E, Ramirez A, *et al.* Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. *EMBO J* 2001; 20:2619–2630.
45. Artandi SE, Alson S, Tietze MK, *et al.* Constitutive telomerase expression promotes mammary carcinomas in aging mice. *Proc Natl Acad Sci USA* 2002; 99:8191–8196.
46. De Jesus BB, Schneeberger K, Vera E, *et al.* The telomerase activator TA-65 ■ elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging Cell* 2011; 10:604–621.  
This study and the one below demonstrate the effects of telomerase treatment in adult mice, either via adenovirus expressing telomerase or using a telomerase activator. Telomerase activation contributes to increased 'healthspan' and longevity, reducing age-related morbidity without increasing cancer incidence.
47. Bernardes de Jesus B, Vera E, Schneeberger K, *et al.* Telomerase gene ■ therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med* 2012; 4:691–704.  
See Ref. [46 ].