Review

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The common biology of cancer and ageing

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Abstract

At first glance, cancer and ageing would seem to be unlikely bedfellows. Yet the origins for this improbable union can actually be traced back to a sequence of tragic—and some say unethical—events that unfolded more than half a century ago. Here we review the series of key observations that has led to a complex but growing convergence between our understanding of the biology of ageing and the mechanisms that underlie cancer.

Like so many areas of science, our subject is one that has no true beginning, and as yet, no clear ending. However, if we must begin somewhere, it would be in the winter of 1951, when a 31-yr-old woman and mother of five small children underwent a seemingly routine biopsy for a suspicious cervical mass. A portion of that biopsy went as usual to the pathology lab for diagnosis; unbeknownst to the patient, another portion was diverted to the research laboratory of two investigators at Johns Hopkins, George and Martha Gey. The Geys had spent the better part of the preceding twenty years attempting to find a human cell that could grow indefinitely in laboratory culture conditions. That search would end with the arrival of this particular biopsy sample. Unfortunately for the patient, the pathology laboratory quickly confirmed that the mass was indeed cancer and, despite surgery and radium treatment, the patient succumbed to her disease a mere eight months later. On the day of her death, in October 1951, George Gey appeared on national television in the United States to announce that a new era in medical research had begun. For the first time, he explained, it was now possible to grow human cells continuously in the laboratory. He termed the cell line he had created the 'HeLa cell', in memory of Henrietta Lacks, the unfortunate young mother whose biopsy sample made all this possible.

Over the next 50 years, researchers would slowly strip away many of the secrets of how a cancer cell achieves and maintains its immortality. Here we review those efforts in an attempt to give both a historical perspective and an update on the more recent experimental highlights. In particular, we will focus on five aspects of cancer biology that appear to be particularly informative about normal ageing: the connection between cellular senescence and tumour formation; the common role of genomic instability; the biology of the telomere; the emerging importance of autophagy in both cancer and ageing; and the central roles of mitochondrial metabolism and energetic-dependent signal transduction in both processes. Together, these findings seem to indicate that both cancer and ageing represent complex biological tapestries that are often—but not always—woven by similar molecular threads.

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Cellular senescence as a block to tumour formation

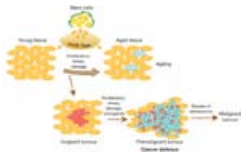
The Geys' success in cultivating human cancer cells spurred a huge interest in isolating as many types of human cells as possible. These early 'cell culturists' quickly recognized that few, if any, of the isolated cell lines maintained a diploid status. This problem led Leonard Hayflick and Paul Moorhead to turn their attention to a

particular source of tissue that is now off limits to many scientists. Using human fetal explants, these investigators found that it was possible to grow and maintain normal diploid fibroblasts. Hayflick and Moorhead emphasized that such isolates were not clonal cell lines, but polyclonal pools or strains[1]. Despite their success in growing these cell lines for several months, they soon stumbled upon another curious phenomenon: cells could not be subcultivated more than about 50 times. They noted that the culture medium was not to blame because if they took early passage cells and transferred them to the conditioned media from late passage cells "luxurious growth invariably results." On the basis of this and other arguments, such as the fact that frozen cells retained the memory of their subcultivation history, they concluded that some intrinsic factor/s (later termed 'Hayflick factors') accumulated in these cells until they 'senesced'[1]. In a further leap of speculation, they proposed that this cellular phenomenon could be relevant for organismal ageing. The degree of that relevance remains hotly debated, although it is now clear that the senescent response can be triggered by a wide variety of cellular stresses including the loss of telomeres, the de-repression of the cyclin-dependent kinase inhibitor 2a (*CDKN2a*, also known as *INK4a* or *ARF*) locus, or the accumulation of DNA damage and the subsequent activation of the DNA damage response. Furthermore, the critical executioners of senescence in response to the above factors seem to include the well known tumour suppressor pathways that are controlled by retinoblastoma 1 (RB1) and P53, proteins that have been widely implicated in tumorigenesis.

The *CDKN2a* locus encodes two separate proteins including p16INK4a, which regulates RB1 activity by directly inhibiting the cyclin-dependent kinases, and p19ARF, which regulates the function of P53. Soon after the initial discovery of p16INK4a (ref. 2) it was observed that the levels of p16INK4a increased progressively with the proliferative history of cells in culture[3, 4]. Moreover, it was found that the expression of certain oncogenes accelerated the de-repression of the *CDKN2a* locus, a phenomenon that was called 'oncogene-induced senescence'[5, 6]. Since then, a wealth of data has supported a model in which cells 'memorize' excessive mitogenic stimulation and cell divisions, in part through the de-repression of the *CDKN2a* locus. The mechanistic details of how this happens are starting to emerge, and seem in part to involve the progressive loss of repressive Polycomb complexes[7]. Genes of the Polycomb family encode highly conserved but poorly understood proteins that seem to epigenetically repress many target genes by regulating the level of histone methylation.

The relevance of senescence for cancer protection can be rationalized if senescence is considered as a stress-induced barrier that limits the proliferative potential of damaged cells. In keeping with this notion, recent data have shown that there are abundant senescent cells within tumours, thus moving these observations from the realm of the plastic plate into the arena of real cancer biology[5, 6] (Fig. 1). This intra-tumoral senescence is thought to be triggered mainly by oncogenic signals that can function in part by de-repressing the *CDKN2a* locus. Another crucial mediator of oncogene-induced senescence seems to be the activation of the DNA damage response (DDR) pathway, presumably by the hyper-replication that is characteristic of cancer cells[8, 9]. With regards to *in vivo* senescence, the hierarchy and crosstalk between induction of the *CDKN2a* locus and the activation of the DDR are not well understood. Another recent surprise was the rapid *in vivo* clearance of tumour cells that undergo P53-triggered senescence[10, 11]. At least in one system, this clearance seems to occur through the activation of the innate immune system[10]. This is relevant because standard chemotherapy and radiotherapy might function in part by inducing senescence within the tumour mass[12]. In addition, other evidence indicates that the immune system's recognition of tumour cells might require the continuous activation of the DDR pathway[13]. Although they are intriguing, such observations need to be placed in the appropriate context, as it is clear that most human malignancies develop in the presence of a functional immune system. Similarly, tissues that undergo normal ageing can accumulate significant numbers of senescent cells, seemingly without provoking a robust immunological response[14, 15].

Figure 1: The potential interplay between stem cells, stress, ageing and cancer.



During normal ageing, stem cells accumulate damage and subsequent stress-dependent changes (for example, de-repression of the *CDKN2a* (*INK4a*/*ARF*) locus or telomere shortening). This leads to the increasing abundance of senescent cells (large blue cells) within differentiated tissues. Incipient tumours, arising directly from stem cells or from more committed cells, undergo rapid proliferation (small red cells). These pre-malignant tumour cells rapidly accumulate damage, in part owing to the presence of oncogenes, leading to a higher proportion of tumour cells becoming senescent (small blue cells). Tumour progression to full malignancy is favoured when tumour cells acquire mutations that impair the senescence program (for example, mutations in *Trp53* or *CDKN2a*).

High resolution image and legend (208K)

The *CDKN2a* locus is normally expressed at very low levels in most tissues of young organisms[16]. It is well established that the *CDKN2a* locus is activated during organismal ageing in both rodents and humans, and the levels of p16INK4a constitute an impressively good overall biomarker of ageing[16, 17]. Interestingly, strategies such as caloric restriction, which extend lifespan, also seem to reverse the age-dependent increase in p16INK4a transcription[16, 18]. The suggestion that p16INK4a is not just a marker but a true effector of ageing remains unproven; however, two independent lines of evidence seem to support this idea. First, a recent spurt of human genetic data indicates that single nucleotide polymorphisms (SNPs) near *CDKN2a* might be associated with ageing and age-related pathologies. Indeed, variants within or near *CDKN2a* were initially associated with overall physical frailty[19] and, more recently, with certain known age-related conditions such as the risk of myocardial infarction[20, 21]. A second line of evidence has centred on the connection between p16INK4a and stem cell biology. Such a link was suspected on the basis of the analysis of mice that are deficient in certain Polycomb genes, which normally repress p16INK4a. These Polycomb-deficient animals seem to have severe defects in stem cell self-renewal[22]. Interestingly, age-induced expression of p16INK4a in adult stem cells seems to be associated with widespread impairment in tissue regeneration[23, 24, 25]. Further reinforcing this link, mice that lack p16INK4a have increased regenerative potential in diverse niches including the nervous system, the pancreas and the haematopoietic system. These observations point to p16INK4a both serving as a break for the proliferation of cancer cells, and also limiting the long-term renewal of stem cells. As such, excessive inhibition of pathways that are linked to cancer might reduce the robustness of various stem cell niches. In essence, cancer prevention might come at the expense of an accelerated decline in tissue regeneration and repair. Although such notions might seem depressing, as discussed below, it is important to note that not every strategy that could protect us from cancer comes at the expense of accelerating ageing.

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Genomic instability links cancer and ageing

The maintenance of DNA represents a fundamental and continuous challenge to every cell. Although a full description of the mechanisms underlying DNA repair and

genomic stability are outside the scope of this review, suffice it to say that there exist multiple distinct pathways to sense and repair damaged DNA, depending on the nature of the damage (including, for instance, whether one or both strands of DNA are involved) and on the phase of the cell cycle in which the damage occurs. Given that genomic instability is a hallmark of most cancers, it is not too surprising that many of the factors that have been implicated in sensing and responding to DNA damage are altered in human tumours. Perhaps less well appreciated is that genomic instability is also a hallmark of ageing. For instance, in budding yeast, the mother cell can give rise to a smaller daughter cell a finite number of times, termed the replicative lifespan. Interestingly, as the mother yeast cell ages, there is a striking increase in genomic instability, as shown by marked loss of heterozygosity (LOH) in the daughter cell[26]. A similar age-dependent increase in chromosomal instability has been known to occur in mammals for many years[27]. Recent evidence indicates that the age-dependent accumulation of somatic mutations might vary significantly between different tissues of the same organism and that these genetic alterations might contribute to the stochastic variation in gene expression that is often seen in mammalian ageing[28].

The molecular analysis of human inherited cancer syndromes such as Li-Fraumeni syndrome, ataxia-telangiectasia (AT) and common forms of familial breast and ovarian cancer have strengthened the link between the maintenance of genome integrity and cancer susceptibility. These conditions can be caused by germline mutations in the genes for P53, the ataxia-telangiectasia mutated (ATM) kinase and breast cancer 1 (BRCA1), respectively—three proteins that are essential in the surveillance of DNA damage. Interestingly, all three proteins have also been linked to cellular or organismal ageing. In the case of p53, mice that are genetically engineered to express altered isoforms of p53 with increased activity seem to be resistant to cancer but age prematurely[29, 30]. As in all models of accelerated ageing, these results are potentially instructive but extension of their lessons to normal ageing must be done with care. Indeed, this accelerated ageing phenotype might be unique to expression of these altered forms of 'superactive' p53, as simple transgenic overexpression of full-length p53 using its endogenous promoter to regulate expression does not result in a change in lifespan[31]. It is conceivable that normally regulated p53 could have a beneficial impact on longevity by eliminating DNA damage (or DNA-damaged cells). In support of this notion, mice in which both p53 and p19Arf are overexpressed show delayed ageing[32], and recent work in *Caenorhabditis elegans* indicates that many lifespan-extending mutations converge on the activation of the worm form of p53 (ref. 33). In a similar vein, a role for the ATM kinase in cellular lifespan was recently established when it was noted that mice lacking *Atm* show rapid ageing and depletion of their haematopoietic stem cell compartment[34]. Finally, although mice with deletion in *Brca1* die as embryos, mice that express two copies of a hypomorphic *Brca1* allele along with only one copy of the gene for p53 ($Trp53^{+/-}$) survive but show marked progeroid symptoms[35]. In each of these cases, ageing is the apparent result of either a chronic increase in the level of DNA damage (ATM and BRCA1 deficiency) or the presumed chronic engagement of DNA damage signalling ('superactive' p53).

Recently, the analysis of mice with targeted deletions or humans with inherited deficiencies in various factors that are involved in sensing or repairing DNA damage have significantly strengthened the correlation between DNA damage and the rate of ageing. For instance, reducing the level of various mitotic checkpoint genes leads to chromosomal instability, augmented aneuploidy and the phenotypic appearance of progeroid mice[36, 37]. Similarly, mice lacking the DNA helicase excision repair cross-complementing rodent repair deficiency, complementation group 2 (Ercc2, also known as Xpd), an enzyme that participates in nucleotide excision repair (NER), show aspects of accelerated ageing[38]. In addition, a recent report of a single patient with a severe mutation in another NER enzyme, ERCC4 (also known as XPF), showed that this patient also exhibited progeroid features[39]. Milder mutations in *ERCC4* were previously known to cause the cancer predisposition syndrome xeroderma pigmentosum, a condition that produces a substantial increase in the propensity for various solid tumours. Together these observations indicate that severe deficiencies in proteins that are involved in DNA damage sensing and DNA repair might accelerate ageing, while milder mutations in these same pathways might predispose individuals to cancer. The mechanism for ageing in the absence of faithful DNA repair is not entirely clear but might be secondary to the induction of senescence or apoptosis of crucial stem and progenitor cells. Alternatively, the absence of DNA repair might cause enough direct damage to fully differentiated cells to impair overall homeostasis. By contrast, milder mutations in the same set of genes might allow cells to survive and proliferate, but with an underlying impairment in DNA fidelity that ultimately predisposes to cancer. This may help us to understand why so many mouse models with deletions of genes linked to repairing or sensing DNA damage can exhibit both cancer susceptibility and progeroid features[40].

Up to now we have discussed a set of genes that were intensively studied because of a known role in cancer or because they were directly implicated in maintaining genomic stability, and which have been linked to ageing much more recently. Nonetheless, those investigators whose primary focus was studying the molecular basis of ageing have also found a strong reason to focus on genomic stability. This interest in large part came about by pursuing curious observations made more than 100 years ago by two young physicians. In 1904, Otto Werner described four siblings, all of whom had an inexplicable set of symptoms including premature greying of the hair, ageing of the skin, growth retardation and the loss of subcutaneous fat. In the same year, Hastings Gilford coined the term 'progeria' to describe a single case of a teenage boy whose outward appearance suggested that he was considerably older then his stated age of fourteen. A century later, the gene responsible for Werner syndrome was identified and demonstrated to belong to the RecQ helicase family. This family of enzymes is conserved from *Eschericia coli* to man, and humans have five RecQ homologues that have important roles in recombination, the replication stress response and maintaining genomic stability. Given that the gene responsible for Werner syndrome (*WRN*) participates in multiple aspects of DNA homeostasis, it is unclear precisely how the absence of WRN activity in affected individuals results in the clinical progeroid syndrome. One attractive explanation is that WRN is essential for proper telomere maintenance through its interaction with the telomeric binding proteins TERF1 and TERF2[41]. Recent information indicates that the *WRN* gene is often inactivated by epigenetic means in human cancers[42], indicating that genes that were identified initially as regulating ageing might also inform us about cancer biology. Similarly, the gene responsible for the progeroid Hutchinson-Gilford syndrome has also been identified, and there is evidence that its product helps to maintain nuclear architecture and to regulate genomic stability[43].

Finally, another family of genes that has been intensely studied for its role in ageing seems also to have an important function in maintaining genomic stability. This family of proteins is termed the sirtuins, a named based on the family's founding member, the yeast protein silent information regulator 2 (Sir2). In yeast, Sir2 has been implicated in the increase in lifespan that is seen after caloric restriction and in both yeast and worms, overexpression of Sir2 is sufficient to extend lifespan. One common feature of the sirtuins is their enzymatic function as NAD-dependent deacetylases and for yeast Sir2, this biochemical activity is required for the proteins' ability to regulate silencing, recombination and genomic stability[44]. Seven mammalian sirtuins have been identified, with the closest mammalian homologue to yeast Sir2 being Sirt1. Establishing a role of Sirt1 in epigenetic silencing and genomic stability has been challenging, because mice with targeted deletion of Sirt1 usually die shortly after birth. Nonetheless, evidence from cell culture models indicates that Sirt1 is involved in heterochromatin formation and might be particularly important in the silencing of certain tumour suppressors[45, 46]. Interestingly, mice with a targeted deletion in Sirt6 manifest an accelerated ageing phenotype that on a cellular level is accompanied by genomic instability and defects in DNA repair[47]. It therefore seems that certain members of the mammalian sirtuin family are essential for maintaining genomic integrity, and one could speculate that their absence might eventually be shown to predispose to tumour formation. Curiously, $Sirt6^{-/-}$ mice also have severely reduced levels of circulating insulin-like growth factor 1 (IGF-1). Although currently unexplained, this result is interesting because insulin–IGF signalling is known to regulate lifespan in lower organisms. The *Sirt6*-deficient mice therefore add to a growing but poorly understood connection between genomic instability and altered IGF-1 signalling, as insulin–IGF signalling is also perturbed in other mouse models of accelerated ageing, including animals with increased p53 activity[30] and mice lacking the NER enzyme ERCC4[39].

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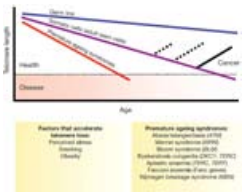
Telomeres and telomerase

Telomeres are specialized structures at the ends of chromosomes, which were first discovered by Barbara McClintock and Herman Müller in the 1930s on the basis of their ability to distinguish natural chromosome ends from broken chromosomes. Müller first termed these structures telomeres (from the Greek word for 'end part'). Telomeres protect natural chromosome ends from fusion events and are therefore essential for chromosomal stability. However, it was not until after the discovery of the structure of DNA that James Watson and Alexey Olovnikov realized that the replication of the very ends of chromosomes, or telomeres, would probably be impaired because conventional DNA polymerases needed a primer to initiate DNA synthesis. This problem came to be known as the 'end-replication problem' and its solution—or lack thereof—provides yet another link between cancer and ageing.

Molecular insight into the nature of telomeres was not gained until they were first sequenced in *Tetrahymena thermophila* by Joe Gall and Elizabeth Blackburn[48]. Telomeres were found to consist of tandem G-rich repeats that expanded until the chromosome end. Cloning of additional telomeres revealed that they are highly conserved in most eukaryotic organisms, with the exception of some flies. The identification of telomeres rapidly led to the realization that some cells could elongate pre-existing telomeres, implying the existence of telomere elongation mechanisms[49]. This telomere elongation was proposed to rely either on recombination events between telomeres or on the existence of a novel enzymatic activity that could synthesize telomere repeats *de novo*. Such an enzymatic activity was soon discovered by Carol Greider and Elizabeth Blackburn and was named telomerase[50]. A few years later, recombination mechanisms were also shown to maintain and elongate telomeres in the absence of telomerase, the so-called alternative lengthening of telomeres (ALT) pathway[51, 52].

Most adult cells have limiting amounts of telomerase that are not sufficient to prevent telomere loss, resulting in the shortening of telomeres with age[53]. As telomeres are essential for chromosomal stability, this progressive telomere loss was proposed to be at the basis of cellular senescence and ageing in the 'telomere hypothesis'[53]. Indeed, telomere length has been shown to predict the replicative capacity of human cells and the appearance of certain age-associated pathologies in humans[54, 55]. The final demonstration that telomere shortening was one of the causes of cellular senescence came from the observation that re-introduction of the *TERT* telomerase gene was sufficient to bypass replicative senescence and to confer immortal growth on a number of human primary cell lines[56]. Furthermore, the generation and characterization of the telomerase knockout mouse model has been instrumental in demonstrating that short telomeres result in multiple organismal defects caused by defective tissue regeneration[57, 58, 59]. In particular, telomerase-deficient mice with short telomeres show reduced function of various stem cell compartments including those in the bone marrow and skin[58, 60]. Interestingly, patients who have inherited or acquired genetic defects that limit telomere maintenance seem to be at substantially increased risk of a range of conditions including aplastic anaemia[61], idiopathic pulmonary fibrosis[62, 63] and the rarer dyskeratosis congenita syndrome[64] (Fig. 2).

Figure 2: Revisiting the telomere hypothesis: role of telomeres in cancer and ageing.



Normal somatic cells, including adult stem cells, suffer progressive telomere attrition coupled to cell division or to increasing age of the organism. This attrition has been proposed to contribute to multiple age-related pathologies. In germline cells, telomere shortening is attenuated owing to high levels of telomerase activity. By contrast, telomere shortening is accelerated in several human premature ageing syndromes, and patients with dyskeratosis congenita and aplastic anaemia show decreased telomerase activity and shortened telomeres owing to mutations in the *TERC* and *TERT* telomerase genes. Psychosocial and environmental factors such as perceived stress, social status, smoking and obesity have also been shown to accelerate telomere attrition. In contrast to normal somatic cells, most immortalized cultures cell lines and more than 95% of human tumours aberrantly activate telomerase to achieve immortal growth. Although telomerase activity has been shown to be rate-limiting for mouse ageing and lifespan, it is unknown whether increased telomerase activity will be able to extend the lifespan of organisms.

High resolution image and legend (157K)

It remains unclear whether increased telomerase activity can delay or prevent ageing phenotypes in the context of the whole organism. First generation mice lacking the telomerase RNA component Terc show a decrease in both their median and maximum lifespan, and these effects become more pronounced with each subsequent generation[65]. The increase in degenerative defects with each subsequent generation that is seen in the Terc-deficient mice is known as 'disease anticipation'. This phenomenon is also observed in some patients with dyskeratosis congenita, and is likely to be seen in patients with aplastic anaemia or pulmonary fibrosis due to telomerase deficiencies. As such, ageing or organ failure in these patients might ultimately result from the inheritance of both impaired telomere maintenance machinery and initially shortened telomeres. Conversely, these findings also support the fascinating idea that the manipulation of telomerase activity might increase the life span of mammals. One caveat to such an approach is the observation that increased telomerase activity in two independent *Tert* transgenic mouse models seemed to increase the susceptibility for tumour formation[66, 67]. In spite of their increased mortality due to cancer, these transgenic mice did show evidence of improved tissue regeneration as well as a slight increase in maximum life span[68]. Interestingly, Tert overexpression can also improve the ability of epidermal stem cells to regenerate the skin and the hair[60, 69].

Over the last decade it has become clear that most human cancers activate telomerase at some point during tumorigenesis, while this activity is largely absent in most normal tissues[70, 71]. A significant number of human tumours can also maintain telomeres by recombination-based ALT mechanisms in the absence of telomerase[72]. By activating a program of telomere maintenance, tumour cells can escape from replicative senescence; this ability was undoubtedly essential for establishing the original HeLa cell line and for most, if not all, immortalized cells thereafter. Conversely, mice with short telomeres are resistant—with a few exceptions—to tumours[73], arguing that telomere shortening represents a potent *in vivo* tumour suppressor mechanism.

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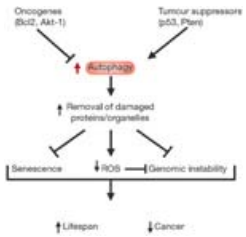
Autophagy and the cell biology of waste management

The ultimate disposition of cellular waste provides another area in which the biologies of cancer and ageing have merged. One particular area of overlap centres on a process known as autophagy. Originally described in yeast, macroautophagy is the process whereby old and damaged proteins and organelles, including mitochondria, are sequestered into double-membraned structures known as autophagosomes. The autophagosome can then fuse with the lysosome in mammalian cells—or with the vacuole in yeast—to further degrade the used cargo back to reusable building blocks. Genetic screens in yeast have identified more than 16 separate and well conserved genes that are required for autophagy to proceed[74]. Relatively little is known about what regulates the rate and selectivity of autophagy. One universal activator of autophagy is a decrease in nutrient availability and this stimulation occurs, at least in part, by the inhibition of TOR (target of rapamycin) signalling[74].

Although the accumulation of damaged proteins and organelles is a hallmark of ageing and age-related diseases, the link between this process and cancer was, until recently, less clear. The first link between autophagy and cancer came with the observation that the product of the mammalian gene beclin 1 (*Becn1*), a homologue of the yeast autophagy gene *VPS30* (also known as *ATG6*), bound to the human oncogene B-cell CLL/lymphoma 2 (BCL2)[75]. Furthermore, the binding of BCL2 to beclin seems to inhibit the autophagy program. This raised the interesting possibility that, in tumours characterized by increased BCL2 expression, the oncogene was working at least in part by suppressing autophagy. Further support of this notion came from mice engineered to have lost one copy of the *Becn1* gene. In this case, the haploinsufficient mice developed tumours, indicating that autophagy might act as an important *in vivo* tumour suppressor[76, 77]. This notion is also supported by observations that in human malignancies the *BECN1* locus is commonly deleted and by experimental evidence that several tumour suppressors, including the phosphatase and tensin homologue Pten and p53, stimulate autophagy[78]. Indeed, although the available evidence indicates that oncogenes can inhibit autophagy and tumour suppressors can stimulate it, the exact mechanistic link between cancer and autophagy remains obscure (Fig. 3). One possibility is that interfering with the normal degradation of organelles leads to the retention of older, damaged mitochondria that serve as a source for damaging reactive oxygen species. Such a mechanism would provide a strong connection between common insults that could both contribute to cancer and accelerate ageing.

Figure 3: The potential role of autophagy in cancer and ageing.



Autophagy is a regulated process for the removal of damaged proteins and organelles. Autophagy occurs under basal conditions and is stimulated by environmental factors such as starvation. There is evidence that proteins that are linked to tumorigenesis can regulate the rate of autophagy, with oncogenes in general blocking and tumour suppressors stimulating the process. The removal of damaged cellular components, especially damaged mitochondria, might decrease the level of reactive oxygen species (ROS), which in turn might reduce genomic instability or forestall cellular senescence. Such mechanisms might allow moderate increases in autophagy to reduce the incidence of cancer and prolong lifespan.

High resolution image and legend (90K)

Recent experiments using mouse knockouts of various autophagy genes have provided considerable insight into the normal physiological role of autophagy, and indicate that this process contributes to certain age-related pathologies. Mice lacking autophagy-related gene 5 (*Atg5*) are born normally but subsequently die within the first 24 h of life[79]. This death is a result of the inability of these mice to activate the macroautophagy program that is required for energy homeostasis immediately after birth. The short lifespan of these mice obviously precludes analysis of whether they also show accelerated ageing or a cancer predisposition phenotype. Nonetheless, two subsequent studies that used brain-specific conditional knockouts of *Atg5* and *Atg7* revealed that, in these animals, the absence of autophagy leads to a shortened lifespan and an accelerated form of age-related neuronal degeneration[80, 81]. Perhaps the strongest link between autophagy and ageing comes from experiments performed in *C. elegans*. In this organism, loss-of-function mutations in the *daf-2* locus extend lifespan. In the worm, daf-2 is an insulin/IGF receptor that regulates not only lifespan but also entry into the alternative developmental pathway known as dauer. When developing worms are faced with unfavourable environmental conditions such as limited nutrients, they can enter a state akin to suspended hibernation known as the dauer diapause. Indeed, the environmental conditions that stimulate dauer entry and the conditions that stimulate autophagy are outwardly similar. Interestingly, both dauer formation and lifespan extension by daf-2 have been shown to require the worm orthologue of beclin[82]. Although these results are clearly informative, the role of autophagy in regulating lifespan in purely postmitotic organisms such as *C. elegans* might be considerably more important than in more complex, renewable mammalian systems where there is normally constant cellular proliferation and cell turnover.

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Metabolism links cancer and ageing

In relatively simple organisms such as *C. elegans*, mutations that prolong lifespan are often intimately connected with the ability of the organism to withstand stress, particularly oxidative and metabolic stress. This same stress resistance might also be important to a rapidly growing tumour cell, where the supply and availability of nutrients and oxygen are often precarious. This strategic metabolic overlap has been made more concrete by observations of specific genes that link together the triad of lifespan, cancer and energetics. One such gene is *Trp53*, which encodes p53. We have mentioned that this tumour suppressor is one of the most frequently mutated genes in human cancers and that there is evidence that increased p53 activity can accelerate ageing. Nonetheless, there is a growing link between p53 and cellular metabolism. This link has been strengthened by recent reports that p53 regulates the transcription of two proteins, TP53-induced glycolosis and apoptosis regulator (TIGAR) and the SCO cytochrome oxidase deficient homologue 2 (SCO2), which have key roles in the utilization of glucose and mitochondrial respiration, respectively[83, 84]. Another pathway that allows cells and organisms to adapt to changes in nutrient availability is the TOR signalling network. This pathway has been the subject of many reviews[85, 86]. For our purpose, suffice it to say that TOR is activated in the presence of abundant nutrients, and inactivated under starvation. A number of the upstream regulators of TOR including PTEN, tuberous sclerosis 2 (TSC2), v-akt murine thymoma viral oncogene homologue 1 (AKT-1) and serine/threonine kinase 11 (STK11, also known as LKB1) are frequently altered in human tumours. Similarly, the use of the TOR inhibitor rapamycin is currently being actively pursued as a treatment for human malignancies[85]. The TOR pathway has also received renewed interest for its role in ageing. In many organisms, decreased TOR signalling is associated with the extension of life span[87, 88, 89]. Similarly, under some conditions, TOR signalling seems to be required for the longevity benefits of caloric restriction in yeast[89].

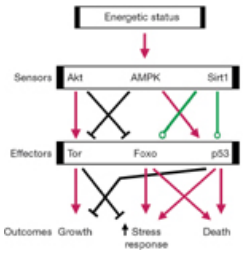
Similarly, in mammalian cells, mammalian TOR (mTOR) seems to be an important regulator of overall mitochondrial metabolism[90].

The family of forkhead transcription factors represents yet another pathway in which cancer, ageing and metabolism intersect. We have previously discussed the long lived *daf-2* mutants in *C. elegans*. Characterization of this pathway revealed that longevity mutations in the daf-2 pathway ultimately function by increasing the activity of the forkhead transcription factor daf-16. Interestingly, the transcriptional targets of daf-16 include a number of enzymes that are involved in metabolism as well as stress resistance[91]. Regulation of daf-16 is in part determined by the subcellular location of the protein and, in worms, the translocation of daf-16 from the cytosol to the nucleus depends on the availability of nutrients. In mammals, the forkhead family members also regulate numerous aspects of cell fate. The closest mammalian orthologue of daf-16 is Foxo3, and there is evidence that this mammalian transcription factor also controls the expression of multiple genes involved in stress resistance and metabolism[91]. There is also growing evidence that mammalian forkhead family members act as tumour suppressors and regulators of mammalian stem cell lifespan[92, 93, 94].

Analysis of a very rare tumour that occurs in the carotid body, called a paraganglioma, has led to another interesting link between metabolism, cancer and ageing. The carotid body is located in the neck and serves to stimulate breathing when there is an increase in blood levels of CO_2, or when there is a decrease in O_2 and/or pH. In one large Dutch family with an inherited paraganglioma syndrome, linkage studies revealed a mutation in one allele of the nuclear gene that encodes subunit D of succinate dehydrogenase (SDH)[95]. Subsequent analysis showed that similar SDH mutations could be found in certain pheochromocytomas, a related tumour in the adrenal gland. In addition, analysis of other unrelated families with paragangliomas showed that in these individuals, tumours were associated with mutations in other SDH subunits. SDH is involved in two aspects of metabolism: it functions as an enzyme in the Krebs cycle (converting succinate to fumarate) as well as serving as complex II of the electron transport chain. Interestingly, inherited mutations in fumarate hydratase, another Krebs cycle enzyme, have also been linked to a separate and equally rare inherited cancer syndrome[96]. In both of these cases, tumours seem to arise secondary to an increase in metabolic intermediates (succinate and fumarate, respectively). These intermediates seem to function, in part, by directly inhibiting the prolyl hydroxylase enzyme family, which controls the degradation of hypoxia inducible factor 1α (HIF1α). Interestingly, in lower organisms such as *C. elegans* and *Drosophila melanogaster*, mutations within the same SDH complex can produce an accelerated ageing phenotype[97, 98]. By contrast, knockdown experiments that target other components of the electron transport chain, including essential elements of complexes I, III and IV, lead to lifespan extension in worms[99, 100]. It is unclear why certain mutations in the electron transport chain shorten the life span while others seem to increase it. An attractive but unproven hypothesis is that accelerated or delayed ageing correlates with the level of mitochondria reactive oxygen species that are produced, based on both where and how (for example, knockdown versus structural mutation) the electron transport chain is inactivated.

Finally, we have for the sake of clarity talked about these various pathways in a linear fashion. There is a growing awareness that, as far as the cell is concerned, sensing nutrient availability and energetic status is an integrated and 'system biology' endeavour[101]. There are many connections between p53, mTOR, Foxo proteins and HIF1-α. For instance, several of these proteins interact directly with each other, and others either share common upstream activators or undergo similar post-translational modification by molecules such as Sirt1 (Fig. 4).

Figure 4: Energy signal transduction.



A complicated web of interactions exists for proteins involved in coordinating energy status with the cell's ultimate fate. Included among these are proteins whose activities seem to be influenced by energetic stores including Akt, AMP-activating protein kinase (AMPK) and the NAD-dependent deacetylase Sirt1. In turn, these sensors can regulate the activity of downstream effectors such as the target of rapamycin (TOR) serine/threonine kinase, the Foxo family of transcription factors and the tumour suppressor p53. Regulation can be positive (red arrows), negative (black lines) or a more subtle change in which some but not all activities are altered (green lines). Overall lifespan seems to be influenced by many of these sensors and effectors, indicating that there is an intimate connection between energy sensing and longevity[101].

High resolution image and legend (116K)

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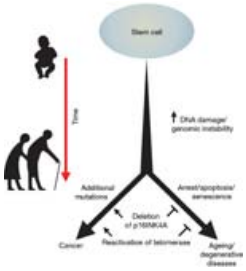
Henrietta's gift

The complexity of ageing and the biology of cancer do not lend themselves to easy generalizations. As we have discussed, in some instances, such as cellular senescence or telomere shortening, strategies that protect us from cancer might hasten our rate of ageing. In other situations, such as autophagy or protection from genomic instability, cancer and ageing seem to share common, rather than antagonistic, aetiologies. In the coming years, it is to be hoped that researchers will further discern how and where these two entities coalesce and where their mechanisms diverge. Indeed, most of the fundamental questions remain unanswered. Among these is whether DNA damage represents the ultimate stimulus to both cancer and ageing. If so, is it the damage itself or the subsequent response to DNA damage that fuels ageing? Similarly, does the steep age-related increase in cancer incidence suggest that cancer is just one of a host of age-related pathologies? Or do the 'superactive' p53 mouse and the recent data on stem-cell deletion of the p16INK4a tumour suppressor indicate that mechanisms that limit the growth of cancer cells will also be rate-limiting for normal stem cells? If the latter is true, will any strategy to increase our molecular vigilance against cancer always come at the expense of limiting tissue regeneration and maintenance? Alternatively, can we view cancer and ageing as pure stem cell diseases, with cancer representing the effect of additional growth promoting mutations within a given stem cell and ageing representing the natural exhaustion and depletion of the stem and progenitor pool (Fig. 5)? Finally, will a deeper understanding of the molecular control of energy sensing and utilization, including what regulates mitochondrial activity and how the nucleus, mitochondria and cytoplasm communicate, provide new and fundamental insights into how we age and how a cancer cell emerges?

Figure 5: A stem cell perspective on cancer and ageing.



A simplified model that views ageing and cancer from the perspective of alterations within the stem and progenitor cell pool. Over the lifespan of an organism, long-lived cells (such as stem cells) accumulate DNA damage from a number of stresses including intracellular oxidants generated from normal metabolism. The default pathway for such damaged stem cells is to undergo growth arrest, apoptosis or senescence. As more and more stem cells withdraw from the proliferative pool, there is a decrease in the overall number and/or functionality of both stem and progenitor cells. This decrease predisposes the organism to impaired tissue homeostasis and regenerative capacity and could contribute to ageing and age-related pathologies. Presumably, some rare cells can escape from this normal default pathway by acquiring additional mutations that allow them to continue to proliferate even in the setting of damaged DNA. These proliferating but damaged cells might provide the seeds for future malignancies. In this scenario, both cancer and ageing result primarily from accumulating damage to the stem and progenitor cell compartment. Mutations that allow stem cells to continue to proliferate in the setting of normal growth arrest signals such as DNA damage (for example, loss of p16INK4a or reactivation of telomerase) would temporarily expand the stem cell pool and hence delay age-related pathologies. Over the long term, these mutations would also increase the likelihood of cancer.

High resolution image and legend (109K)

Undoubtedly, none of these questions were contemplated on that day in October 1951 when Henrietta Lacks's body was laid to rest in an unmarked grave near her family's small tobacco farm. Unbeknownst to those who gathered in that Virginia field—but as we now know—not all of Henrietta was buried that day. The small part that remained in the laboratory would forever change the course of science and help lead us to a clearer understanding of the barriers that separate normal cells from their cancer counterparts. These same barriers now appear to be intimately connected to how and why we age. Perhaps Henrietta's final gift to us is the growing realization that somewhere within the curse of the cancer cell's immortality there might also lie the secret of how we might understand and extend our own lifespan.

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Competing interests statement

The authors declare no competing financial interests.

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