OPINION

How ageing processes influence cancer

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Abstract | The ageing of populations worldwide is leading to an unprecedented increase in cancer cases and fatalities. Understanding the links between cancer and ageing is therefore more important than ever. How the interplay of ageing-associated changes affects cancer initiation and progression is complex, however, and some ageing processes probably foster cancer development whereas others hinder it, possibly in a tissue-specific manner. In the emerging age of cancer, how can our growing understanding of the biology of ageing inform cancer biology?

Ageing is the biggest risk factor for cancer; the majority of tumours (in developed countries) are diagnosed in aged patients[1,2], and this is projected to be the global scenario by 2050 (REF. 3). The connection between cancer and ageing has been well-documented in numerous epidemiological studies[4]. After sexual maturity, cancer incidence increases exponentially with age (FIG. 1a). Given the ageing of the population in modern societies, it is not surprising that the burden of cancer is now the highest in human history and will continue to increase for the foreseeable future[5,6]. However, the relationship between the biology of cancer and that of ageing is far from clear. According to the widely accepted multistep model of cancer in which various sequential mutations are required for a cell to become malignant, exposure time to a known or unknown carcinogen (or carcinogens) is a risk factor for cancer, and some authors have long argued that by itself this explains the increased risk of cancer with age[1,7]. However, recent evidence from a variety of ageing studies demonstrates that there is at least some overlap between ageing and cancer processes: epidemiological data show that familial factors are associated with both low cancer occurrence and longevity[8]. Furthermore, various genetic and dietary manipulations that slow ageing in rodents also reduce cancer incidence[9,10] and vice versa[11], and host tissue susceptibility to cancer changes with age[9].

Although the age-related increase in cancer risk is well-established, the age-related patterns of cancer are far from straightforward[4,12]; for example, cancer incidence levels off at advanced ages (FIG 1a,b). Additionally, cancer morbidity and mortality have been reported to decline in the oldest age group, including in centenarians[13]. Even though the exact reasons for this are unknown, the decline in overall cancer-associated mortality may be caused by an age-related decrease in the heterogeneity of the population, as seems to occur during ageing[14], whereby subpopulations that are prone to higher mortality die at younger ages, leaving individuals that are less susceptible to cancer in older age groups. The rate of age-related increase in cancer incidence also varies between cancer types with, for example, prostate cancer incidence accelerating much faster than brain cancer (FIG. 1b). Some cancers have early-life incidence peaks, such as osteosarcoma and acute lymphoblastic leukaemia[4,9], and the incidence of testicular cancer peaks at approximately age 30 years and then sharply declines (FIG. 1c). The incidence of other tumour types, such as cervical cancer, also levels off at middle age (FIG. 1d). Exposure to risk factors early in life, such as infectious diseases, could have a role in early-life peaks in cancer incidence, yet as the probability of cells becoming malignant is expected to increase with age, some inversely age-associated cancers, such as testicular cancer, seem to have no established explanation.

Apart from accumulating mutations, normal ageing causes many changes that may increase susceptibility to cancer initiation and/or create a tissue microenvironment that is more propitious for the growth of malignant cells, thus favouring cancer progression and metastases[9]. Ageing processes, including cell senescence and alterations to endocrine and immune systems, are possible explanations, although contentious, that are discussed herein. The broad aim of this article is to paint a picture of what we know and which crucial questions remain unanswered concerning the biological links between cancer and ageing.

Alterations to ageing affect cancer

Ageing is a complex process that entails multiple phenotypes: physiological and molecular changes that contribute to the degeneration and functional decline with age of practically all organs and body systems, increased susceptibility to various diseases and exponentially increasing mortality with age[15]. In spite of its complexity, one of the most exciting discoveries in biogerontology is the surprising plasticity of ageing[10,16]. According to GenAge: the Ageing Gene Database, hundreds of genes have been shown to modulate longevity in model organisms, including approximately 100 in mice[17]. Most genetic and dietary manipulations that affect ageing in rodents also have an impact on cancer incidence and/or progression[9], suggesting overlapping mechanisms (FIG. 2). For example, mice with extra copies of *Trp53* (which encodes p53) and cyclin-dependent kinase inhibitor 2A (*Cdkn2a*; which encodes INK4A and ARF) exhibit strong cancer resistance, in addition to slightly increased longevity and lower levels of ageing-associated oxidative damage[18].

Life-extending genetic alterations. In rodents, typically mice, single gene manipulations have been shown to increase lifespan by up to 50%[17] and to retard various physiological and molecular aspects of ageing phenotypes. The fact that ageing as a whole, including multiple age-related changes and diseases, can be manipulated in rodents by single genes shows that ageing is not merely a collection of pathological processes running in parallel but rather that there are processes capable

of synchronizing and driving the progression of ageing in mammals[15]. As such, most of these genetic manipulations in mice also retard cancer incidence and development[9]. Notably, mutant mice with disrupted growth hormone (GH; also known as somatotropin) and insulin-like growth factor I (IGF1) signalling are long-lived and tend to have a smaller body size, decreased cancer incidence and often longer cancer latency compared with wild-type mice[9]. For example, one study found that a population of growth hormone receptor (*Ghr*)-knockout mice were less frequently tumour-bearing than wild-type controls (68% versus >90%, respectively), they also developed fewer different tumours, less frequently died of neoplastic diseases (42% compared with 83% in wild-type littermates) and had less-severe neoplastic lesions, although this was only significant for pulmonary adenocarcinoma[19]. A similar study in Ames dwarf mice, which are GH-deficient owing to an underdeveloped pituitary gland, found no differences in tumour incidence between Ames dwarf mice and wild-type controls[20]. However, fatal neoplastic disease occurred later in life in Ames dwarf mice, and the severity of lung adenocarcinoma was lower compared with wild-type littermates, thus suggesting a delayed progression of fatal neoplastic disease in Ames dwarf mice[20]. This cancer-protective effect may not be surprising given that lower GH–IGF1 signalling results in less cell proliferation *in vivo*[21]. Interestingly, reducing the stimulus for cell proliferation can not only reduce cancer incidence but can also extend lifespan in mice[22], and therefore mouse models of ageing may be useful for cancer studies.

Humans with *GHR* mutations, which result in GHR deficiency (also known as Laron syndrome) and low serum levels of IGF1 and IGF2, are also protected against cancer: among 30 individuals studied, no cancer deaths were observed compared with ~20% of deaths in relatives with no GHR deficiency[23]. Contrary to *Ghr*-knockout mice, which are long-lived[24], GHR deficiency in humans does not seem to extend lifespan, possibly because it is associated with an increased risk of heart diseases and with non-age-related causes of death[23]. Epidemiological studies also suggest that short, small people tend to have a slightly lower cancer incidence, which could again reflect the association between reduced cell proliferation and cancer incidence[25].

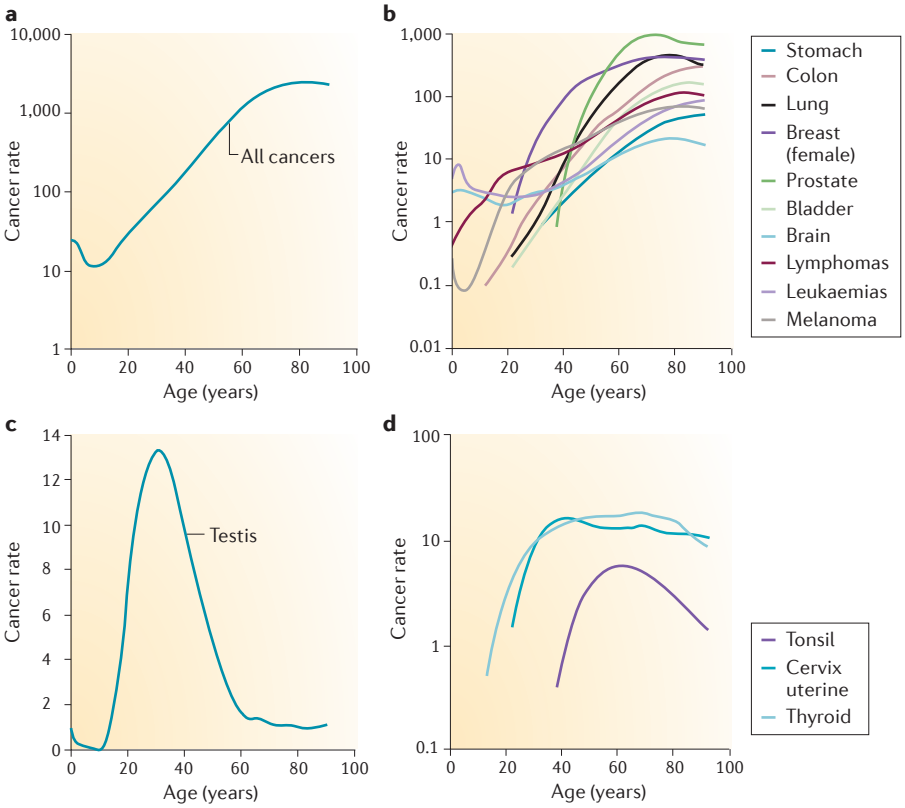

Figure 1 | **The incidence of cancer diagnosis as a function of age.** Cancer rate (per 100,000 people, in a logarithmic scale) from the entire United States population (1999–2009) by age for: all cancers (**a**); selected sites in which cancer incidence increases exponentially with age after maturity (**b**); testicular cancer (**c**); and selected sites in which cancer incidence peaks relatively early in life (**d**). Unless otherwise stated and unless for gender-specific cancers, data from males and females were combined. Data are from the United States Cancer Statistics, Wide-ranging Online Data for Epidemiologic Research (WONDER) database[133].

Accelerated ageing and cancer. Numerous genetic manipulations in mice, and a few human diseases, have been classified as putative cases of accelerated ageing. Human progeroid syndromes include Werner syndrome, Hutchinson–Gilford syndrome and Cockayne syndrome. Patients with these syndromes exhibit signs and features of ageing at a relatively young age, including premature death, although none of these diseases is a perfect phenocopy of ageing[26]. Of these three classical human progeroid syndromes, predisposition to cancer is only strongly observed in patients with Werner syndrome[26], although these patients develop different tumour types, in particular a higher ratio of sarcomas to carcinomas, when compared with the normal population[27]. Many progeroid syndromes in mice and humans originate from mutations that disrupt DNA repair and/or DNA damage responses, resulting in an increased incidence of tumours that usually occur at a decreased latency[9]. Various authors have recently reviewed this topic and its relevance to cancer and ageing[9,26,28,29]. The fact that disruption of DNA repair and/or DNA damage responses results in signs of premature ageing and often cancer predisposition gives weight to the idea that DNA changes with age are an important factor for cancer and ageing. Even though premature ageing is often associated with cancer susceptibility in mice and humans, exceptions exist, such as in Cockayne syndrome in which patients do not exhibit cancer predisposition[26,28,29]. Likewise, not all mouse models of disrupted DNA repair systems result in accelerated ageing. One emerging picture is that disruption of specific DNA repair pathways is associated with ageing, cancer or both[26,28,30]. In particular, it has been argued that disruption of pathways that result in the accumulation of DNA damage and mutations, such as global genome nucleotide excision repair (NER), predisposes to cancer, whereas disruption of DNA repair pathways resulting in loss of proliferative capacity or overall cell loss, such as transcription-coupled NER, often drives ageing[28].

Calorific restriction and the effects of diet on cancer and ageing. In addition to genetic manipulations of ageing, dietary manipulations also have a substantial impact on

cancer and ageing in animal models. The most widely studied life-extending intervention is calorific restriction (CR), which consists of restricting calorie intake without inducing malnutrition. CR extends lifespan in most species, and has been shown to significantly increase lifespan (by up to 50%) in mice and rats, although not in all strains[10]. Numerous studies in rodents have shown a marked reduction in cancer incidence from CR[31], even in naturally occurring long-lived strains[32] and when CR is started in 1-year-old, middle-aged mice[33,34]. One study found that when CR in mice was initiated late in life (19-month-old animals), overall cancer incidence was not affected but the growth of tumours was reduced[35].

Two studies in rhesus monkeys, which did not encompass the whole lifespan as some animals are still alive, reported a decreased incidence of neoplasia in animals under CR[36,37]. When CR was initiated late in life, neoplasia incidence was not reduced[37], in line with the studies of mice[35], although it is unknown whether CR can delay tumour growth in monkeys. The two studies in monkeys contradict each other in terms of mortality: one study at the Wisconsin National Primate Research Center (WNPRC) showed a marked decrease in mortality owing to CR[36], which was not observed in another study conducted at the US National Institute on Aging (NIA)[37]. Conflicting results between studies could be due to differences in the controls' diets, as the controls in the NIA study were fed a healthier diet. For example, in the NIA study, food intake of control animals was slightly restricted to prevent obesity[37]. Cancer, diabetes and cardiovascular disease were the most prevalent age-related diseases observed in controls in both studies, yet a decreased incidence of cardiovascular disease in monkeys under CR was only observed in the WNPRC study[36,37].

Obesity and excess adipose tissue have been associated with a shorter lifespan and with various age-associated diseases in humans, including cancer[1,38–40]. Some of the health benefits of CR, including anticancer effects, could therefore be due to reduced fatness. Intriguingly, however, mouse strains with the least fat reduction under CR tend to exhibit life-extension and vice versa[41]; whether these effects of CR correlate with cancer incidence is not known, and it may be that excessive fat reduction is unhealthy in mice, yet these results question the role of fat reduction in CR effects.

Although the molecular mechanisms underlying CR remain the subject of debate, some evidence points towards a role for the GH–IGF1 pathway (FIG. 2), the activity of which is decreased in rodents undergoing CR and in long-lived strains[10,24,31,42]. High IGF1 levels have been associated with tumour progression[43]. In a p53-deficient mouse model of bladder cancer, the restoration of IGF1 levels in mice undergoing CR prevented the slowing of tumour progression[44]. Not surprisingly, animals undergoing CR are smaller, and the lack of mitogenic stimuli may help to explain the observed protection from cancer. Other potential molecular mechanisms of CR include: the mTOR pathway, which extends lifespan in animal models and might have a role in CR; the energy sensor AMP-activated protein kinase (AMPK), which has been associated with longevity and CR in invertebrates; and sirtuins, for example SIRT1, which has been hypothesized to be a key player in CR[10,39]. However, the role of SIRT1 in mammalian ageing and CR remains controversial, with mixed results from rodents[10,45]. The overexpression of SIRT1 in mice does not extend lifespan but seems to protect against some types of cancer[46], so a role for SIRT1 in the anticancer effects of CR cannot be excluded, as further discussed below. The PI3K pathway, and various players associated with it including AKT, PTEN and mTOR (FIG. 2), have long been associated with ageing in model systems[16] and may be part of the signalling cascade involved in CR[10]. Given its role in the regulation of the cell cycle, the PI3K pathway is an attractive target for anticancer therapies[47] and might mediate the anticancer effects of CR.

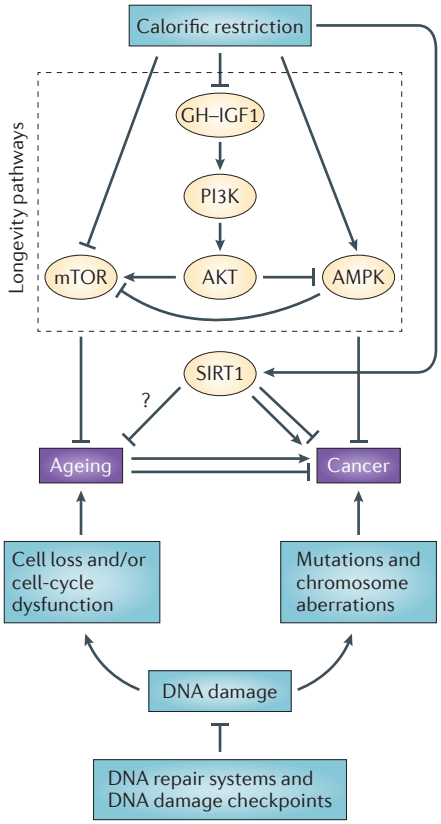

Figure 2 | **Major longevity pathways with overlapping effects on ageing and cancer.** The growth hormone (GH)–insulin-like growth factor I (IGF1) pathway and its signalling cascade, which involves PI3K and AKT, can modulate longevity and cancer in model systems. Calorific restriction inhibits GH–IGF1 signalling and can also inhibit mTOR and activate AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1). Interactions between components of these pathways, and with SIRT1, remain incompletely understood. The role of SIRT1 in modulating mammalian ageing has not been demonstrated, and it seems to have a dual role in cancer. DNA repair systems and DNA damage checkpoints prevent the DNA damage accumulation that contributes to cancer and ageing, although possibly through different cellular mechanisms.

Shared cancer and ageing mechanisms

The probability of tumour formation may increase with age simply because exposure time increases, yet ageing-associated phenotypes also seem to have a role in the increased incidence of cancer. However, a major open question is: are ageing-associated processes and changes making host tissues more or less susceptible to tumour initiation, progression and metastasis? Some of the processes that are thought to be most important are discussed below.

DNA damage responses. It is undeniable that DNA damage, mutations and genome instability increase with age[26,28,48]. Recent large-scale studies have begun to quantify this increase in humans: one study using blood and buccal samples found a low frequency (0.23%) of detectable clonal mosaicism until age 50, which then gradually increased with age up to 1.9% in individuals aged 75–79 years[49]; another study found similar results[50]. However, human studies have been restricted to a small number of tissues, and much more detailed studies have been conducted in mice[9,12,26,48]. Using transgenic mice with *lacZ* or *lacI* to measure the mutation frequency, various studies have found that the accumulation of mutations can occur from early in life, but they also found large differences in the rates of mutation accumulation between tissues[48,51–53]. Although the accumulation of mutations with age in mice is highest in the small intestine, and can be observed in the liver, heart and most organs, it was not observed in the testis and brain[48,51–53]. However, a more recent study found that

point mutations accumulate in subparts of the brain, namely the hippocampus and hypothalamus[54]. Of note, the accumulation of mutations seems to be organ-specific and not clearly related to organ proliferative capacity[48]. Clearly, as more cells accumulate more mutations with age, the probability of developing cancer increases. A role of epigenetic changes has also been hypothesized because both global hypomethylation and promoter hypermethylation have been reported in both ageing and cancer[55]. For example, hypermethylation of the RAS association domain family 1 (*RASSF1*) promoter is associated with cancer and is also observed to increase with age and with adiposity[56].

Evidence is emerging that DNA repair pathways become less efficient with age, although the mechanisms involved are unknown[26,57]. There also seems to be age-related changes in susceptibility to carcinogens[12]. Studies by Anisimov and others[9,12] in over 20 different tissues reveal conflicting findings; exposure to carcinogens in aged mice resulted in increased cancer development compared with younger controls in some tissues but not in others. For example, 15-month-old female rats exposed to *N*-nitroso-*N*-methylurea (NMU) had a higher frequency of tumours of the corpus and cervix uteri and a lower frequency of mammary and intestinal adenocarcinomas and tumours of the ovary and kidney than 3-month-old animals exposed to NMU[58]. These mixed results might be explained by age-associated differences in susceptibility to carcinogens owing to changes in the activity of enzymes that are necessary for carcinogen activation or changes in proliferative activity that occur with ageing in a tissue-specific manner.

If the idea is correct that DNA damage accumulation is a major driver of ageing-associated phenotypes, then DNA damage would represent an overlapping mechanism between tumorigenesis and ageing (FIG. 2), even though, as aforementioned, different types of DNA repair and DNA lesions may be more relevant to each process. The various progeroid syndromes that result from mutations that disrupt DNA repair pathways give strength to the idea that DNA damage is not simply associated with ageing but may have a causal role. One recent study found that overexpression in mice of BUB1B, which is a mitotic checkpoint protein that controls chromosome segregation and maintains genetic stability, protects against cancer and extends healthy lifespan[11], although further work is necessary to prove that reducing DNA damage retards ageing[26].

Telomeres, replicative senescence and tissue homeostasis. Telomeres (which are repetitive sequences at the ends of chromosomes) shorten with cell division in normal human somatic cells and limit replicative potential *in vitro*[59]. Because they can limit cell proliferation, telomeres have long been hypothesized to be a causal factor in ageing. Short telomeres activate DNA damage response pathways that cause cells to undergo irreversible growth arrest (cell senescence). Cellular stress, such as DNA damage, can also trigger senescence in a process termed stress-induced premature senescence[60,61]. It is widely accepted that telomere shortening evolved as a tumour-suppressive mechanism, and disruption of players in the pathways that lead to replicative senescence are associated with cancer[59,61,62]. Moreover, the observation that large, long-lived species tend to have short telomeres and low levels of telomerase (which is the enzyme that maintains telomere length) suggests that short telomeres and telomerase suppression are necessary for the evolution of large body sizes and longevity, presumably by suppressing cancer[63].

> “replicative senescence may render old tissues more fertile grounds for cancer development”

A more controversial issue is the role of telomere shortening and replicative senescence in whole-organism ageing (reviewed in REFS 59–61). Several studies, including in humans, have observed telomere shortening *in vivo* during ageing[59]. Likewise, senescent cells have been reported to accumulate with age in many mammalian tissues, and have also been observed in some pathological conditions such as atherosclerosis[64] and benign prostatic hyperplasia[65], although whether such senescent cells contribute pathologically is unknown, as they may merely reflect damage to tissues[60,61]. One study found that the number of senescent fibroblasts increases exponentially with age in the skin of baboons, with senescent cells comprising >15% of cells in very old animals compared with ~2% in young animals[66]. The incidence of senescent cells has also been found to increase in aged mouse tissues, such as in the liver[67], although it is possible that cell senescence in mice is induced through telomere-independent mechanisms because mice have relatively long telomeres[68]. Likewise, markers of replicative senescence, such as the expression of the tumour suppressor INK4A — in which genetic variants have been associated with other age-related diseases such as heart failure and type 2 diabetes[59] — have been found in the tissues of old mice[69,70]. One hypothesis is that senescent cells impair tissue renewal and homeostasis, decrease organ function and thus contribute to ageing, although this hypothesis remains contentious.

Even if the issue of whether replicative senescence is a cause of ageing-associated phenotypes remains open, evidence suggests that senescent cells accumulate in some tissues with age and that these cells might contribute to cancer development. Telomere shortening and the resulting telomere dysfunction has been suggested to contribute to cancer susceptibility by increasing the risk of chromosomal aberrations caused by breakage–fusion–bridge cycles[71]. Furthermore, mice with short telomeres have a higher incidence of cancer[72], including in p53-deficient mice[73], possibly because of increased genetic instability caused by loss of telomere function.

In spite of its role as a tumour-suppressive mechanism, replicative senescence may render old tissues more fertile grounds for cancer development. Campisi and colleagues[74] have shown that senescent cells can secrete pro-inflammatory cytokines, extracellular matrix components and other factors that disrupt the tissue microenvironment and promote tumorigenesis. Specifically, senescent human fibroblasts in culture stimulate the proliferation of premalignant and malignant epithelial cells, but not of normal cells[74]. Interestingly, immunocompromised mice injected with premalignant or malignant epithelial cells together with senescent cells form more and larger tumours than with epithelial cells alone or with presenescent control cells[74–76]. Using a *Cdkn2a*^{INK4A}–luciferase reporter mouse model, one recent study found an exponential increase in INK4A expression with age, and the induction of INK4A was observed in the benign stromal cells of the nascent neoplasm. However, total-body INK4A expression did not predict overall mortality or the development of spontaneous malignancy[77], which does not support a causal role for senescent cells in ageing or in tumorigenesis.

One recent study in mice reported that the clearance of senescent cells expressing INK4A delays ageing-associated phenotypes, such as lordokyphosis, sarcopenia and cataracts[78]. However, it is important to note that the clearance of senescent cells in the transgenic progeroid mice used in this study did not extend lifespan. Therefore, although this study provides evidence that senescent cells may cause age-associated phenotypes in

this model, whether senescent cells contribute to normal ageing-associated phenotypes remains unknown. However, transgenic mice in which senescent cells can be inducibly ablated may allow researchers to evaluate whether the presence of senescent cells in aged tissues facilitates cancer development. Such models may also help to unravel the functions of senescent cells because it remains largely unknown why these exist in the first place — why not just trigger cell death?

Endocrine changes with age. Systemic changes during ageing may contribute to cancer susceptibility. For example, endocrine changes with ageing may decrease cancer risk: sex hormones, such as oestrogens and androgens, are known to contribute to some types of cancer[79], and their levels typically decline with age, thus potentially offering some protection from cancer[6]. Moreover, GH and IGF1 levels decline with age[80,81]. As detailed above, low GH–IGF1 signalling has been associated with decreased cancer incidence, and thus one hypothesis is that these endocrine changes contribute to hinder cancer development in old age.

The ageing immune system. It is well-established that the immune system becomes compromised during ageing (known as immunosenescence), with inflammation increasing with age[82,83]; in fact, mononuclear cells of healthy elderly people exhibit increased cytokine production[84]. Ershler and colleagues[85,86] have argued that immunosenescence will decrease host susceptibility to cancer because of the role of the immune system in driving tumour growth. By contrast, immunosurveillance also becomes compromised with age, and this may contribute to the increased cancer development in old age[87]. However, the evidence for either scenario is far from conclusive, and the impact of immunosurveillance on fighting cancer is unclear. For example, although immunocompromised patients have a higher cancer incidence, it is not clear whether this is due to reduced immunosurveillance or a higher incidence of tumours caused by infectious agents[1].

It is now recognized that inflammation has a role in cancer aetiology, and various studies have found that inflammation can have tumour-promoting effects (reviewed in REFS 88,89). Inflammation is an established hallmark of ageing: the circulating levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor (TNF), are increased at older ages[83,90], and inflammatory gene expression signatures are observed across aged mammalian tissues[91]. For example, higher levels of IL-6 and TNF have been associated with the prevalence of colorectal adenomas[92]. It is also interesting to note that higher levels of inflammatory cytokines are associated with fat mass and obesity[90,93], which might contribute to the increased cancer incidence among obese individuals, and body fat as a percentage of body weight increases with age[94]. It is therefore tempting to speculate that the increased inflammatory environment of ageing tissues may favour cancer development.

Vascular ageing and angiogenesis. Because tumour vascularization is essential for the growth of solid tumours, vascular ageing has been proposed to contribute to a decline in the angiogenic potential of aged tissues, which hinders the progression of solid tumours in old age[86]. Some evidence from mice supports this view: it has been reported that the slower growth of some tumour cells in older mice when compared with that in younger animals may be related to a reduced capacity to vascularize tumours[95,96], which may be further augmented by short telomeres[97]. Slower tumour growth and reduced tumour vascularity were also observed in mice with genetically induced atherosclerosis (apolipoprotein E (*Apoe*)$^{-/-}$ mice) than in young or non-atherosclerotic mice, suggesting that vascular ageing and disease can affect tumour progression[96].

Are old tissues fertile ground for cancer?

Given that mutations accumulate with age, aged tissues will tend to have a higher number of cells in an advanced stage of carcinogenesis, and this is a major factor in the observed increased cancer incidence with age[9,12]. Indeed, when *Trp53* is deleted in mice of different ages, a shorter latency of tumour development results when the gene is ablated in older animals, which may be explained by wild-type p53 keeping in check a growing number of oncogenically activated cells with age[98]. A more controversial issue is whether ageing-associated changes contribute to create a more fertile ground for cancer development rather than cancer occurring simply because the probability of tumour initiation increases with time. By contrast, if normal processes that are often hijacked by tumours degenerate with age then this may confer cancer protection. This pivotal issue of whether ageing processes create a more or less fertile ground for cancer has not been studied in a systematic manner, and the studies conducted to date provide contradictory evidence.

In the classic study of Peto *et al.*[99] the authors found that exposing mice to carcinogens resulted in the induction of cancer that was independent of the age of the animals. Peto *et al.* interpreted these results as evidence that cancer development is independent of ageing[99], although the oldest mice used were only ~1 year of age, and thus they may not have been sufficiently old for any differences to be observed. As discussed above, more recent results have been mixed, and there seem to be carcinogen-specific and tissue-specific effects of ageing.

Other studies have used xenografts to study tumour growth in animals of different ages. Again, systematic studies are lacking and results are contradictory, yet substantial effects of ageing have been observed[100]. These effects vary between tumour types; for example, one prostate cancer cell line grows as quickly in old mice as in young mice[101]. Ershler *et al.*[102] found that B16 mouse melanoma cells grow considerably faster and form more tumour colonies in younger mice, whereas another study found reduced proliferation and increased apoptosis of rat liver tumour cells in young rats relative to old rats[103].

In humans, the commonly held belief that cancer is less aggressive in older patients has not been demonstrated for most types of cancer (FIG. 3); several tumour types are more aggressive in old age[6,86,100]. For example, the prognosis of acute myeloid leukaemia[104] and of ovarian cancer[105] is worse in the elderly. By contrast, the prognosis for breast cancer is worst for young women and best for middle-aged (45–49 years old) women[106]. However, the poorer prognosis in elderly individuals (FIG. 3) may also be related to confounding factors, such as less aggressive treatment. Another caveat of human clinical

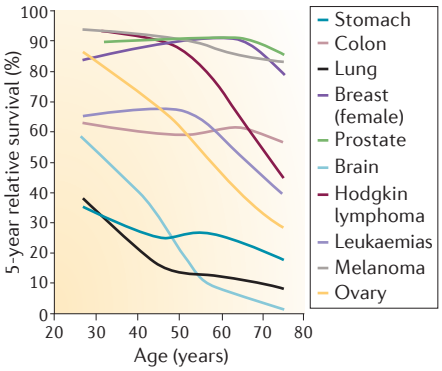

Figure 3 | **Cancer survival as a function of age.** Five-year relative survival with age for selected sites. Data are for patients in England, UK, diagnosed 2006–2010 and followed-up until 2011. Unless otherwise stated and unless for gender-specific cancers, data from males and females were combined. Data are from the UK Office for National Statistics.

data is that tumours often have different genetic backgrounds between young and old patients with cancer, and it is therefore not possible to compare tumours that develop in individuals with similar genetic backgrounds at different ages.

Overall, several studies in rodents have shown substantial effects of ageing on the tumour host. However, these studies were conducted using different strains and experimental conditions and unsurprisingly failed to render a clear picture. Some ageing processes seem to act synergistically to promote cancer initiation and growth (such as the accumulation of senescent cells and increased inflammation), whereas others seem to antagonize cancer initiation and growth (such as vascular ageing and a decline in GH levels) (FIG. 4). It is also important to emphasize that the effects of ageing on cancer vary markedly across tumour types and tissues. For example, differences in antigenicity between tumours are likely to be important for determining whether particular tumours may benefit from, or be hindered by, an ageing immune system[6,85,100]. Clearly, the effects of ageing on the tumour host merit a more systematic inquiry.

Applications in the cancer clinic

One of the most exciting prospects in the field is translating findings from the biology of ageing into the clinic[10,31]. Despite its benefits in model organisms, CR is a challenging diet to undergo, and clinical trials are extremely difficult given the length of time required to assess the effects on ageing. Nonetheless, one study found that anorexic women have a lower incidence of breast cancer; like CR, anorexia leads to reduced levels of IGF1 and oestrogens, suggesting that CR may protect against cancer in humans[107]. Fasting in mice reduces IGF1 levels and protects normal cells, but not cancer cells, from the cytotoxic effects of high-dose chemotherapy[108]. The efficacy of fasting before chemotherapy is currently being explored[109].

Small molecules with life-extending properties in model organisms, such as rapamycin and resveratrol, are being tested as treatments against cancer[10]. Although both rapamycin and resveratrol have been studied for their anticancer properties before the discovery of any longevity effects, the finding that resveratrol extends longevity no doubt has put this compound in the spotlight. However, some controversy surrounds resveratrol. Briefly, resveratrol has been shown to extend lifespan only in obese animals, and its putative main target, SIRT1, is equally contentious[10,45]. Studies have shown that SIRT1 may protect mice from colon cancer[110] and breast cancer[111], and SIRT1 activators are undergoing clinical trials for anticancer therapy[10]. However, high levels of SIRT1 have been observed in some tumours, and SIRT1 inhibition also shows promise in anticancer therapies[112], for example in leukaemias in which SIRT1 has been found to be overexpressed[113]. As such, depending on the context, SIRT1 may have oncogenic or tumour-suppressive properties[114].

Rapamycin and the mTOR pathway are another link between ageing and cancer. mTOR inhibition, through treatment with rapamycin or genetic manipulation, has been associated with increased longevity in animal models[10], including in normal[115] and in *Trp53*$^{+/-}$ mice[116]. Another drug that might mimic, at least partly, the beneficial effects of CR is metformin, which is used to treat patients with type 2 diabetes[10]. Metformin activates AMPK via the tumour suppressor liver kinase B1 (LKB1; also known as STK11), and it can inhibit cell growth in an AMPK-dependent manner[117], although in some cell lines mTOR inhibition by metformin has been shown to be AMPK-independent[118]. Epidemiological studies in patients with type 2 diabetes suggest that metformin may decrease cancer risk[119], and metformin is now being explored as a cancer treatment in clinical trials (for example, NCT01101438). Other drugs that are associated with life-extension in mice — such as aspirin, which slightly extends the lifespan of male mice[120] — are also being explored as cancer treatments[121–123].

Overall, studies of ageing can help to focus attention on drug targets for cancer therapies and on the development of anticancer lifestyles, diets and drugs. Mice, even naturally occurring long-lived strains[32], die primarily of cancer[9]. As such, the vast majority of life-extending interventions in mice, including drugs, have an impact on cancer. Thus, these interventions may be useful to study further in terms of potential human applications, either to enhance traditional treatments such as chemotherapy or for prevention in cancer-prone patients.

Concluding remarks

The interplay between cancer and ageing is complex and far from straightforward. The accumulation of mutations with age[49,50] is still widely held as the major driver of the age-related increase in cancer incidence[1,7,9,12]. However, a picture is emerging of how several age-associated changes might foster cancer development in old age, whereas other changes may hinder it (FIG. 4). It is important to note that there is no evolutionary selection for ageing, just as there is no selection for age-related increases in cancer incidence, because individuals are affected after reproductive maturity. Therefore, ageing and cancer have no evolutionary purpose, which contributes to their complexity and entropy, and it is thus not surprising that ageing processes may aid or hinder cancer depending on the tissue and tumour type. Because of this intrinsic complexity of ageing and cancer, I am convinced that we need to move

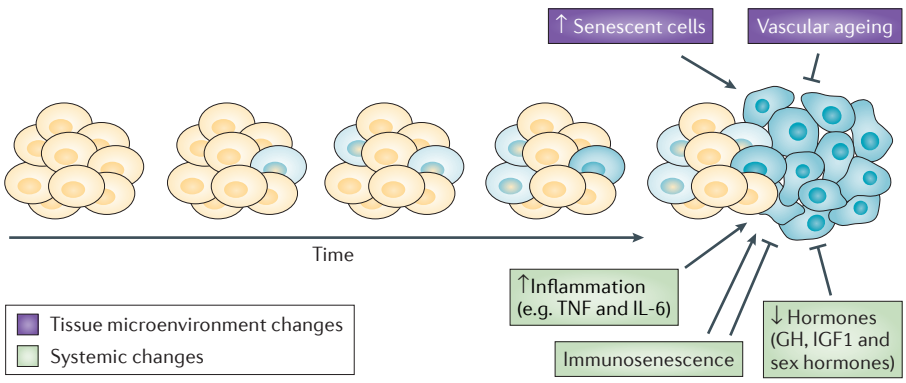

Figure 4 | **The interplay between ageing processes and cancer.** It is well-established that the accumulation of DNA changes (darker cells represent cells with DNA mutations) is the primary process that is responsible for the age-associated increase in cancer incidence. Various other ageing-associated processes also seem to contribute to, or suppress, cancer initiation and growth. These can be divided into age-related changes affecting the tissue microenvironment and systemic changes. Changes to the tissue microenvironment include vascular ageing, which may hinder cancer progression, and the accumulation of senescent cells, which may favour it. Systemic changes include decreasing circulating levels of various hormones, which possibly hinders cancer development, as well as immunosenescence (the role of which in cancer is controversial) and inflammation (which probably favours cancer development). The interplay between these factors, as well as their tissue-specific impact, remains unknown. GH, growth hormone; IGF1, insulin-like growth factor I; IL-6, interleukin-6; TNF, tumour necrosis factor.

Box 1 | **Models of cancer resistance**

Cancer research is largely based on animal models, particularly mice and rats, that develop cancer at a much higher rate than humans do. However, an unexplored paradigm is the use of cancer-resistant organisms to identify genes, mechanisms and processes that protect against (rather than cause) cancer[124,125]. One such organism is the naked mole-rat (*Heterocephalus glaber*), the longest-living rodent that is capable of living for over 30 years[124]. To date, in over 1,000 animals examined, neoplasia has not been observed[126], and thus *H. glaber* must have evolved mechanisms that confer exceptional cancer protection. Cellular studies have begun to reveal possible tumour-suppressive mechanisms in *H. glaber*[127], such as INK4A-mediated hypersensitivity to contact inhibition compared with mouse cells[128], and *H. glaber* cells exhibit resistance to experimental tumorigenesis induced by the expression of the combination of the oncogenes $Hras^{G12V}$ and SV40 large T antigen[129]. Another genus of mole-rats, *Spalax*, are also cancer-resistant and relatively long-lived (maximum longevity of more than 20 years); a mechanism of necrotic cell death in *Spalax* has been recently shown to be initiated to limit proliferation[130]. Lastly, as observed by Peto *et al.*[99], if the chance of each cell becoming malignant is the same, then large, long-lived species such as whales would have an impossibly high probability of developing cancer[125]. For example, the bowhead whale (*Balaena mysticetus*) is the second largest animal on earth and has been estimated to live for >200 years[131]. Therefore, species such as whales, even though they can develop cancer, must have evolved robust antitumour mechanisms compared with humans. Perhaps long-lived and cancer-resistant species undergo a more complex, multistep pathway to tumorigenesis, and more mutations are necessary to produce a lethal cancer. Because all of these species are mammals, most genes will have human homologues, and genome comparisons may help to elucidate mechanisms that are involved in the evolution of longevity and cancer protection[132]. Discovering the 'tricks' that are used in different species to suppress cancer development could lead to a better understanding of cancer mechanisms and may lead to cancer prevention in humans[125].

beyond reductionist approaches and to integrate processes at the molecular, cellular and physiological levels to understand the links between ageing and cancer.

Importantly, a number of questions remain unanswered: why does the incidence of some tumours (for example, testicular cancer) peak early in life? Can we identify genes that protect against cancer from studies in long-lived individuals or long-lived species (BOX 1)? Which tissues does ageing render more and less fertile for tumour formation and why? How do age-related endocrine changes influence cancer development? How does immune-system dysfunction contribute to cancer susceptibility, and does increased inflammation with age contribute to cancer development? Can we translate findings from the biology of ageing (for example, CR) to fight cancer?

Understanding the biological underpinnings of the relationship between cancer and ageing could have broad implications. Strikingly, young rodents are the most widely used animal model of cancer, yet most tumours affect aged people. A systematic, in-depth understanding of the role of ageing processes in cancer is imperative. Taking into account ageing-associated processes may be crucial to develop preventive strategies and effective therapies against cancer. Moreover, substantial age-associated differences in incidence and progression are observed between cancer sites that probably reflect different processes and risk factors that are specific to each tissue and tumour type. Unravelling which factors and ageing-associated processes are more important for oncogenic development in different tissues could allow more personalized cancer treatments.

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1. Peto, J. Cancer epidemiology in the last century and the next decade. *Nature* **411**, 390–395 (2001).
2. Edwards, B. K. *et al.* Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. *Cancer* **94**, 2766–2792 (2002).
3. Parkin, D. M., Bray, F. I. & Devesa, S. S. Cancer burden in the year 2000. The global picture. *Eur. J. Cancer* **37** (Suppl. 8), S4–S66 (2001).
4. Frank, S. A. *Dynamics of Cancer: Incidence, Inheritance, and Evolution* (Princeton (NJ), 2007).
5. Jones, D. S., Podolsky, S. H. & Greene, J. A. The burden of disease and the changing task of medicine. *N. Engl. J. Med.* **366**, 2333–2338 (2012).
6. Balducci, L. & Ershler, W. B. Cancer and ageing: a nexus at several levels. *Nature Rev. Cancer* **5**, 655–662 (2005).
7. Peto, R. & Doll, R. There is no such thing as aging. *BMJ* **315**, 1030–1032 (1997).
8. Christensen, K. *et al.* Cancer and longevity—is there a trade-off? A study of cooccurrence in Danish twin pairs born 1900–1918. *J. Gerontol. A Biol. Sci. Med. Sci.* **67**, 489–494 (2012).
9. Anisimov, V. N. Carcinogenesis and aging 20 years after: escaping horizon. *Mech. Ageing Dev.* **130**, 105–121 (2009).
10. de Magalhaes, J. P., Wuttke, D., Wood, S. H., Plank, M. & Vora, C. Genome-environment interactions that modulate aging: powerful targets for drug discovery. *Pharmacol. Rev.* **64**, 88–101 (2012).
11. Baker, D. J. *et al.* Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. *Nature Cell Biol.* **15**, 96–102 (2013).
12. Anisimov, V. N. The relationship between aging and carcinogenesis: a critical appraisal. *Crit. Rev. Oncol. Hematol.* **45**, 277–304 (2003).
13. Stanta, G., Campagner, L., Cavallieri, F. & Giarelli, L. Cancer of the oldest old. What we have learned from autopsy studies. *Clin. Geriatr. Med.* **13**, 55–68 (1997).
14. Vaupel, J. W. Biodemography of human ageing. *Nature* **464**, 536–542 (2010).
15. de Magalhaes, J. P. in *An Introduction to Gerontology* (ed. Stuart-Hamilton, I.) 21–47 (Cambridge Univ. Press, 2011).
16. Kenyon, C. J. The genetics of ageing. *Nature* **464**, 504–512 (2010).
17. Tacutu, R. *et al.* Human Ageing Genomic Resources: integrated databases and tools for the biology and genetics of ageing. *Nucleic Acids Res.* **41**, D1027–D1033 (2013).
18. Matheu, A. *et al.* Delayed ageing through damage protection by the Arf/p53 pathway. *Nature* **448**, 375–379 (2007).
19. Ikeno, Y. *et al.* Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. *J. Gerontol. A Biol. Sci. Med. Sci.* **64**, 522–529 (2009).
20. Ikeno, Y., Bronson, R. T., Hubbard, G. B., Lee, S. & Bartke, A. Delayed occurrence of fatal neoplastic diseases in Ames dwarf mice: correlation to extended longevity. *J. Gerontol. A Biol. Sci. Med. Sci.* **58**, 291–296 (2003).
21. Ng, S. T. *et al.* Growth hormone treatment induces mammary gland hyperplasia in aging primates. *Nature Med.* **3**, 1141–1144 (1997).
22. de Magalhaes, J. P. & Faragher, R. G. Cell divisions and mammalian aging: integrative biology insights from genes that regulate longevity. *Bioessays* **30**, 567–578 (2008).
23. Guevara-Aguirre, J. *et al.* Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci. Transl Med.* **3**, 70ra13 (2011).
24. Coschigano, K. T. *et al.* Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. *Endocrinology* **144**, 3799–3810 (2003).
25. Gunnell, D. *et al.* Height, leg length, and cancer risk: a systematic review. *Epidemiol. Rev.* **23**, 313–342 (2001).
26. Freitas, A. A. & de Magalhaes, J. P. A review and appraisal of the DNA damage theory of ageing. *Mutat. Res.* **728**, 12–22 (2011).
27. Goto, M., Miller, R. W., Ishikawa, Y. & Sugano, H. Excess of rare cancers in Werner syndrome (adult progeria). *Cancer Epidemiol. Biomarkers Prev.* **5**, 239–246 (1996).
28. Hoeijmakers, J. H. DNA damage, aging, and cancer. *N. Engl. J. Med.* **361**, 1475–1485 (2009).
29. Lombard, D. B. *et al.* DNA repair, genome stability, and aging. *Cell* **120**, 497–512 (2005).
30. Freitas, A. A., Vasieva, O. & de Magalhaes, J. P. A data mining approach for classifying DNA repair genes into ageing-related or non-ageing-related. *BMC Genomics* **12**, 27 (2011).
31. Hursting, S. D., Lavigne, J. A., Berrigan, D., Perkins, S. N. & Barrett, J. C. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu. Rev. Med.* **54**, 131–152 (2003).
32. Harper, J. M., Leathers, C. W. & Austad, S. N. Does caloric restriction extend life in wild mice? *Aging Cell* **5**, 441–449 (2006).
33. Weindruch, R. & Walford, R. L. Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. *Science* **215**, 1415–1418 (1982).
34. Pugh, T. D., Oberley, T. D. & Weindruch, R. Dietary intervention at middle age: caloric restriction but not dehydroepiandrosterone sulfate increases lifespan and lifetime cancer incidence in mice. *Cancer Res.* **59**, 1642–1648 (1999).
35. Dhahbi, J. M., Kim, H. J., Mote, P. L., Beaver, R. J. & Spindler, S. R. Temporal linkage between the phenotypic and genomic responses to caloric restriction. *Proc. Natl Acad. Sci. USA* **101**, 5524–5529 (2004).
36. Colman, R. J. *et al.* Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* **325**, 201–204 (2009).
37. Mattison, J. A. *et al.* Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature* **489**, 318–321 (2012).
38. Calle, E. E. & Kaaks, R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Rev. Cancer* **4**, 579–591 (2004).

39. Longo, V. D. & Fontana, L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol. Sci.* **31**, 89–98 (2010).
40. Flegal, K. M., Graubard, B. I., Williamson, D. F. & Gail, M. H. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* **298**, 2028–2037 (2007).
41. Liao, C. Y. *et al.* Fat maintenance is a predictor of the murine lifespan response to dietary restriction. *Aging Cell* **10**, 629–639 (2011).
42. Breese, C. R., Ingram, R. L. & Sonntag, W. E. Influence of age and long-term dietary restriction on plasma insulin-like growth factor-1 (IGF-1), IGF-1 gene expression, and IGF-1 binding proteins. *J. Gerontol.* **46**, B180–B187 (1991).
43. Grimberg, A. & Cohen, P. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. *J. Cell. Physiol.* **183**, 1–9 (2000).
44. Dunn, S. E. *et al.* Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res.* **57**, 4667–4672 (1997).
45. Herranz, D. & Serrano, M. SIRT1: recent lessons from mouse models. *Nature Rev. Cancer* **10**, 819–823 (2010).
46. Herranz, D. *et al.* Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. *Nature. Commun.* **1**, 3 (2010).
47. Fresno Vara, J. A. *et al.* PI3K/Akt signalling pathway and cancer. *Cancer Treat. Rev.* **30**, 193–204 (2004).
48. Vijg, J. & Dolle, M. E. Large genome rearrangements as a primary cause of aging. *Mech. Ageing Dev.* **123**, 907–915 (2002).
49. Jacobs, K. B. *et al.* Detectable clonal mosaicism and its relationship to aging and cancer. *Nature Genet.* **44**, 651–658 (2012).
50. Laurie, C. C. *et al.* Detectable clonal mosaicism from birth to old age and its relationship to cancer. *Nature Genet.* **44**, 642–650 (2012).
51. Stuart, G. R., Oda, Y., de Boer, J. G. & Glickman, B. W. Mutation frequency and specificity with age in liver, bladder and brain of *lacI* transgenic mice. *Genetics* **154**, 1291–1300 (2000).
52. Dolle, M. E. *et al.* Rapid accumulation of genome rearrangements in liver but not in brain of old mice. *Nature Genet.* **17**, 431–434 (1997).
53. Dolle, M. E., Snyder, W. K., Gossen, J. A., Lohman, P. H. & Vijg, J. Distinct spectra of somatic mutations accumulated with age in mouse heart and small intestine. *Proc. Natl Acad. Sci. USA* **97**, 8403–8408 (2000).
54. Busuttil, R. A. *et al.* Intra-organ variation in age-related mutation accumulation in the mouse. *PLoS ONE* **2**, e876 (2007).
55. Johnson, A. A. *et al.* The role of DNA methylation in aging, rejuvenation, and age-related disease. *Rejuven. Res.* **15**, 483–494 (2012).
56. Peters, I. *et al.* Adiposity and age are statistically related to enhanced *RASSF1A* tumor suppressor gene promoter methylation in normal autopsy kidney tissue. *Cancer Epidemiol. Biomarkers Prev.* **16**, 2526–2532 (2007).
57. Gorbunova, V., Seluanov, A., Mao, Z. & Hine, C. Changes in DNA repair during aging. *Nucleic Acids Res.* **35**, 7466–7474 (2007).
58. Anisimov, V. N. Effect of age on dose-response relationship in carcinogenesis induced by single administration of *N*-nitrosomethylurea in female rats. *J. Cancer Res. Clin. Oncol.* **114**, 628–635 (1988).
59. Collado, M., Blasco, M. A. & Serrano, M. Cellular senescence in cancer and aging. *Cell* **130**, 223–233 (2007).
60. Campisi, J. Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. *Cell* **120**, 513–522 (2005).
61. de Magalhaes, J. P. From cells to ageing: a review of models and mechanisms of cellular senescence and their impact on human ageing. *Exp. Cell Res.* **300**, 1–10 (2004).
62. Finkel, T., Serrano, M. & Blasco, M. A. The common biology of cancer and ageing. *Nature* **448**, 767–774 (2007).
63. Gomes, N. M. *et al.* Comparative biology of mammalian telomeres: hypotheses on ancestral states and the roles of telomeres in longevity determination. *Aging Cell* **10**, 761–768 (2011).
64. Minamino, T. *et al.* Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. *Circulation* **105**, 1541–1544 (2002).
65. Castro, P., Giri, D., Lamb, D. & Ittmann, M. Cellular senescence in the pathogenesis of benign prostatic hyperplasia. *Prostate* **55**, 30–38 (2003).
66. Herbig, U., Ferreira, M., Condel, L., Carey, D. & Sedivy, J. M. Cellular senescence in aging primates. *Science* **311**, 1257 (2006).
67. Panda, S., Isbatan, A. & Adami, G. R. Modification of the ATM/ATR directed DNA damage response state with aging and long after hepatocyte senescence induction *in vivo*. *Mech. Ageing Dev.* **129**, 332–340 (2008).
68. Wang, C. *et al.* DNA damage response and cellular senescence in tissues of aging mice. *Aging Cell* **8**, 311–323 (2009).
69. Molofsky, A. V. *et al.* Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. *Nature* **443**, 448–452 (2006).
70. Krishnamurthy, J. *et al.* p16INK4a induces an age-dependent decline in islet regenerative potential. *Nature* **443**, 453–457 (2006).
71. DePinho, R. A. The age of cancer. *Nature* **408**, 248–254 (2000).
72. Rudolph, K. L. *et al.* Longevity, stress response, and cancer in aging telomerase-deficient mice. *Cell* **96**, 701–712 (1999).
73. Chin, L. *et al.* p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. *Cell* **97**, 527–538 (1999).
74. Krtolica, A., Parrinello, S., Lockett, S., Desprez, P. Y. & Campisi, J. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc. Natl Acad. Sci. USA* **98**, 12072–12077 (2001).
75. Coppe, J. P. *et al.* A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. *PLoS ONE* **5**, e9188 (2010).
76. Liu, D. & Hornsby, P. J. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. *Cancer Res.* **67**, 3117–3126 (2007).
77. Burd, C. E. *et al.* Monitoring tumorigenesis and senescence *in vivo* with a *p16*^{INK4a}-luciferase model. *Cell* **152**, 340–351 (2013).
78. Baker, D. J. *et al.* Clearance of p16^{Ink4a}-positive senescent cells delays ageing-associated disorders. *Nature* **479**, 232–236 (2011).
79. Folkerd, E. J. & Dowsett, M. Influence of sex hormones on cancer progression. *J. Clin. Oncol.* **28**, 4038–4044 (2010).
80. Ho, K. Y. *et al.* Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. *J. Clin. Endocrinol. Metab.* **64**, 51–58 (1987).
81. Hammerman, M. R. Insulin-like growth factors and aging. *Endocrinol. Metab. Clin. North Am.* **16**, 995–1011 (1987).
82. Miller, R. A. The aging immune system: primer and prospectus. *Science* **273**, 70–74 (1996).
83. Franceschi, C. *et al.* Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech. Ageing Dev.* **128**, 92–105 (2007).
84. Fagiolo, U. *et al.* Increased cytokine production in mononuclear cells of healthy elderly people. *Eur. J. Immunol.* **23**, 2375–2378 (1993).
85. Kaesberg, P. R. & Ershler, W. B. The importance of immunesenescence in the incidence and malignant properties of cancer in hosts of advanced age. *J. Gerontol.* **44**, 63–66 (1989).
86. Ershler, W. B. & Longo, D. L. Aging and cancer: issues of basic and clinical science. *J. Natl Cancer Inst.* **89**, 1489–1497 (1997).
87. Swann, J. B. & Smyth, M. J. Immune surveillance of tumors. *J. Clin. Invest.* **117**, 1137–1146 (2007).
88. Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. *Nature* **454**, 436–444 (2008).
89. Colotta, F., Allavena, P., Sica, A., Garlanda, C. & Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* **30**, 1073–1081 (2009).
90. Pedersen, M. *et al.* Circulating levels of TNFα and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. *Mech. Ageing Dev.* **124**, 495–502 (2003).
91. de Magalhaes, J. P., Curado, J. & Church, G. M. Meta-analysis of age-related gene expression profiles identifies common signatures of aging. *Bioinformatics* **25**, 875–881 (2009).
92. Kim, S. *et al.* Circulating levels of inflammatory cytokines and risk of colorectal adenomas. *Cancer Res.* **68**, 323–328 (2008).
93. Fontana, L., Eagon, J. C., Trujillo, M. E., Scherer, P. E. & Klein, S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* **56**, 1010–1013 (2007).
94. Durnin, J. V. & Womersley, J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br. J. Nutr.* **32**, 77–97 (1974).
95. Pili, R. *et al.* Altered angiogenesis underlying age-dependent changes in tumor growth. *J. Natl Cancer Inst.* **86**, 1303–1314 (1994).
96. Klement, H. *et al.* Atherosclerosis and vascular aging as modifiers of tumor progression, angiogenesis, and responsiveness to therapy. *Am. J. Pathol.* **171**, 1342–1351 (2007).
97. Franco, S., Segura, I., Riese, H. H. & Blasco, M. A. Decreased B16F10 melanoma growth and impaired vascularization in telomerase-deficient mice with critically short telomeres. *Cancer Res.* **62**, 552–559 (2002).
98. Hinkal, G., Parikh, N. & Donehower, L. A. Timed somatic deletion of p53 in mice reveals age-associated differences in tumor progression. *PLoS ONE* **4**, e6654 (2009).
99. Peto, R., Roe, F. J., Lee, P. N., Levy, L. & Clack, J. Cancer and ageing in mice and men. *Br. J. Cancer* **32**, 411–426 (1975).
100. Anisimov, V. N. Effect of host age on tumor growth rate in rodents. *Front. Biosci.* **11**, 412–422 (2006).
101. Reed, M. J. *et al.* The effects of aging on tumor growth and angiogenesis are tumor-cell dependent. *Int. J. Cancer* **120**, 753–760 (2007).
102. Ershler, W. B., Stewart, J. A., Hacker, M. P., Moore, A. L. & Tindle, B. H. B16 murine melanoma and aging: slower growth and longer survival in old mice. *J. Natl Cancer Inst.* **72**, 161–164 (1984).
103. McCullough, K. D., Coleman, W. B., Smith, G. J. & Grisham, J. W. Age-dependent induction of hepatic tumor regression by the tissue microenvironment after transplantation of neoplastically transformed rat liver epithelial cells into the liver. *Cancer Res.* **57**, 1807–1813 (1997).
104. Lancet, J. E., Willman, C. L. & Bennett, J. M. Acute myelogenous leukemia and aging. Clinical interactions. *Hematol. Oncol. Clin. North Am.* **14**, 251–267 (2000).
105. Maas, H. A., Kruitwagen, R. F., Lemmens, V. E., Goey, S. H. & Janssen-Heijnen, M. L. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. *Gynecol. Oncol.* **97**, 104–109 (2005).
106. Adami, H. O., Malker, B., Holmberg, L., Persson, I. & Stone, B. The relation between survival and age at diagnosis in breast cancer. *N. Engl. J. Med.* **315**, 559–563 (1986).
107. Michels, K. B. & Ekbom, A. Caloric restriction and incidence of breast cancer. *JAMA* **291**, 1226–1230 (2004).
108. Lee, C. *et al.* Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res.* **70**, 1564–1572 (2010).
109. Safdie, F. M. *et al.* Fasting and cancer treatment in humans: A case series report. *Aging* **1**, 988–1007 (2009).
110. Firestein, R. *et al.* The SIRT1 deacetylase suppresses intestinal tumorigenesis and colon cancer growth. *PLoS ONE* **3**, e2020 (2008).
111. Wang, R. H. *et al.* Interplay among BRCA1, SIRT1, and Survivin during BRCA1-associated tumorigenesis. *Mol. Cell* **32**, 11–20 (2008).
112. Lara, E. *et al.* Salermide, a Sirtuin inhibitor with a strong cancer-specific proapoptotic effect. *Oncogene* **28**, 781–791 (2009).
113. Li, L. *et al.* Activation of p53 by SIRT1 inhibition enhances elimination of CML leukemia stem cells in combination with imatinib. *Cancer Cell* **21**, 266–281 (2012).
114. Brooks, C. L. & Gu, W. How does SIRT1 affect metabolism, senescence and cancer? *Nature Rev. Cancer* **9**, 123–128 (2009).
115. Harrison, D. E. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* **460**, 392–395 (2009).
116. Komarova, E. A. *et al.* Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53$^{+/-}$ mice. *Aging* **4**, 709–714 (2012).
117. Zakikhani, M., Dowling, R., Fantus, I. G., Sonenberg, N. & Pollak, M. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. *Cancer Res.* **66**, 10269–10273 (2006).
118. Kalender, A. *et al.* Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner.

Cell. Metab. **11**, 390–401 (2010).
119. Libby, G. *et al.* New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* **32**, 1620–1625 (2009).
120. Strong, R. *et al.* Nordihydroguaiaretic acid and aspirin increase lifespan of genetically heterogeneous male mice. *Aging Cell* **7**, 641–650 (2008).
121. Algra, A. M. & Rothwell, P. M. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol.* **13**, 518–527 (2012).
122. Rothwell, P. M. *et al.* Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* **379**, 1602–1612 (2012).
123. Dowling, R. J., Goodwin, P. J. & Stambolic, V. Understanding the benefit of metformin use in cancer treatment. *BMC Med.* **9**, 33 (2011).
124. Buffenstein, R. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. *J. Comp. Physiol. B* **178**, 439–445 (2008).
125. Caulin, A. F. & Maley, C. C. Peto's Paradox: evolution's prescription for cancer prevention. *Trends Ecol. Evol.* **26**, 175–182 (2011).
126. Buffenstein, R. The naked mole-rat: a new long-living model for human aging research. *J. Gerontol. A Biol. Sci. Med. Sci.* **60**, 1369–1377 (2005).
127. Seluanov, A. *et al.* Distinct tumor suppressor mechanisms evolve in rodent species that differ in size and lifespan. *Aging Cell* **7**, 813–823 (2008).
128. Seluanov, A. *et al.* Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. *Proc. Natl Acad. Sci. USA* **106**, 19352–19357 (2009).
129. Liang, S., Mele, J., Wu, Y., Buffenstein, R. & Hornsby, P. J. Resistance to experimental tumorigenesis in cells of a long-lived mammal, the naked mole-rat (*Heterocephalus glaber*). *Aging Cell* **9**, 626–635 (2010).
130. Gorbunova, V. *et al.* Cancer resistance in the blind mole rat is mediated by concerted necrotic cell death mechanism. *Proc. Natl Acad. Sci. USA* **109**, 19392–19396 (2012).
131. George, J. C. *et al.* Age and growth estimates of bowhead whales (*Balaena mysticetus*) via aspartic acid racemization. *Can. J. Zool.* **77**, 571–580 (1999).
132. Li, Y. & de Magalhaes, J. P. Accelerated protein evolution analysis reveals genes and pathways associated with the evolution of mammalian longevity. *Age* **35**, 301–314 (2013).
133. United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. *United States Cancer Statistics: 1999–2009 WONDER Online Database* [online] http://wonder.cdc.gov/cancer.html (2013).

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Competing interests statement
The author declares no competing financial interests.

DATABASES
ClinicalTrails.gov: http://www.clinicaltrials.gov
NCT01101438
National Cancer Institute Drug Dictionary:
http://www.cancer.gov/drugdictionary
aspirin | metformin | rapamycin | resveratrol

FURTHER INFORMATION
João Pedro de Magalhães's homepage:
http://pcwww.liv.ac.uk/~aging
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http://genomics.senescence.info/genes

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OPINION

Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance?

Michael Hölzel, Anton Bovier and Thomas Tüting

Abstract | Immunotherapies, signal transduction inhibitors and chemotherapies can successfully achieve remissions in advanced stage cancer patients, but durable responses are rare. Using malignant melanoma as a paradigm, we propose that therapy-induced injury to tumour tissue and the resultant inflammation can activate protective and regenerative responses that represent a shared resistance mechanism to different treatments. Inflammation-driven phenotypic plasticity alters the antigenic landscape of tumour cells, rewires oncogenic signalling networks, protects against cell death and reprogrammes immune cell functions. We propose that the successful combination of cancer treatments to tackle resistance requires an interdisciplinary understanding of these resistance mechanisms, supported by mathematical models.

Normal tissues show a highly structured organization, with specialized cell types residing in well-defined niches to fulfil their physiological functions. For example, the skin consists of the epidermis and the dermis, with numerous blood vessels, nerves, hair roots and several types of glands. Epidermal keratinocytes arise from precursors in stem cell compartments, differentiate, and form the lipid-rich outermost corneal layer as a barrier to the environment and for the prevention of water loss. Pigment-producing melanocytes, which are interspersed in the basal epidermis and the hair follicles, provide protection against ultraviolet (UV) irradiation (FIG. 1a). Skin cancer can result when incorrectly repaired UV-induced DNA damage disturbs growth signalling pathways and cell cycle control mechanisms in epidermal keratinocytes or melanocytes (FIG. 1b). In cancerous tissues, the rules of normal tissue organization are replaced by a new metastable order of aberrant cell proliferation, differentiation and death[1]. Genetically and phenotypically heterogeneous malignant cells engage in novel associations and interdependencies with abnormal fibroblasts, endothelial cells and immune cells in the tumour microenvironment that sustain tumour growth despite fluctuations in nutrient and oxygen supply. Finally, cancer cell invasion and the development of metastases compromise the integrity and survival of the organism as a whole. Indeed, in patients with widely metastatic disease, such as that arising in patients with melanoma, a cure with surgery is no longer possible. The use of systemic treatment approaches to eradicate tumour cells in such patients[2] is likely to disrupt any metastable order that has been established during the long process of tumour evolution (FIG. 1c). The initiation of an injury response results in the recruitment of inflammatory immune cells that normally restores tissue organization under physiological conditions. Unfortunately, in most patients with metastatic disease, tumour regressions and remissions are brief (FIG. 1d). Ultimately, resistance to therapy arises that results in relapse and the death of the patient (FIG. 1e).

Patients with unresectable solid melanoma metastases have been treated with the DNA-damaging agent dacarbazine as the standard of care for many years[2] (FIG. 2a). In the past decade, advances in tumour biology and immunology have led to the development of new rationally designed treatment approaches that impair oncogenic signal transduction pathways — for example, with inhibitors of the BRAF kinase[3–6] (FIG. 2b) — or that strengthen tumour-specific cytotoxic T cell responses — for example, with antibodies that target cytotoxic T lymphocyte protein 4 (CTLA4)[7,8] or programmed cell death protein 1 (PD1)[9,10] (FIG. 2c). When applied as monotherapies, these new treatment strategies could induce responses and remissions, but melanomas frequently relapse. Clinical trials are already under